AD-A061 593 JOHNS HOPKINS UNIV BALTIMORE MD SCHOOL OF HYGIENE A--ETC F/G 6/18
PARENTAL RADIATION AND DOWN'S SYNDROME, WITH PARTICULAR ATTENTI--ETC(U)
JUN 76 B H COHEN DADA17-69-C-0154
UNCLASSIFIED NL

1 OF 5
AD
A061 593

= 5

593

AD-A061593

LEVEL II

PARENTAL RADIATION AND DOWN'S SYNDROME, WITH PARTICULAR ATTENTION TO IONIZING RADIATION AND RADAR

FINAL REPORT

Bernice H. Cohen, Ph.D., M.P.H.

June 30, 1976

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Washington, D. C. 20315

Contract No.: DADA-17-69-C-9154
DAMD-17-75-M-5883
DAMD-17-76-M-5883

Johns Hopkins University
School of Hygiene and Public Health
Baltimore, Maryland 21205

Approved for public release; distribution unlimited

The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents.

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) PARENTAL RADIATION AND DOWN'S SYNDROME, with Particular Attention to Ionizing Radiation and Radar		5. TYPE OF REPORT & PERIOD COVERED FINAL REPORT
		6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) Bernice H. Cohen, Ph.D., M.P.H.		8. CONTRACT OR GRANT NUMBER(s) DADA-17-69-C-9154 new DAMD-17-75-M-5883 DAMD-17-76-M-5883
9. PERFORMING ORGANIZATION NAME AND ADDRESS The Johns Hopkins University School of Hygiene and Public Health Baltimore, Maryland 21205		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
11. CONTROLLING OFFICE NAME AND ADDRESS U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND Washington, D. C. 20315		12. REPORT DATE June 30, 1976
		13. NUMBER OF PAGES 360
14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office)		15. SECURITY CLASS. (of this report) Unclassified
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release; distribution unlimited

ACCESSION for		
NTIS	White Section	X
DDC	Buff Section	☐
UNANNOUNCED		☐
JUSTIFICATION		
BY		
DISTRIBUTION/AVAILABILITY CODES		
Dist.	AVAIL. and/or	SPECIAL
A		

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Down's syndrome, Mongolism, radiation, radar, microwave, chromosomes, genetic, parental factors, cytogenetics, congenital malformations, Trisomy 21

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

To confirm or reject a possible association of Down's syndrome with maternal medical radiation and paternal radar exposure observed in a previous investigation, a replication study was conducted on parents of 300 "Current Series" cases and controls born 1962-1968 and 1945. Validation of military service and radar exposure was undertaken for all Original and Current Series fathers (involving 791 cases, controls and new matches) and chromosomes

studied on 159 radar exposed and unexposed fathers. Current Series findings confirm the association with advancing maternal age and lack of a similar paternal age relationship, but show no case-control differences in parental (maternal or paternal) medical radiation or paternal radar exposure. Combining the series still yielded no significant case-control differences in fathers' radar exposure or military service, although slightly more (NSD) Army service was observed in case fathers of each series. A suggestion of more chromosome aberrancy in radar exposed fathers of the Combined Series must be interpreted with caution. Whether the apparent association indicates greater chromosome fragility with microwave exposure or is otherwise biologically meaningful, or is just spurious, requires more definitive, longitudinal studies.

SUMMARY

PARENTAL RADIATION AND DOWN'S SYNDROME WITH PARTICULAR ATTENTION TO IONIZING RADIATION AND RADAR

To confirm or reject previous findings suggesting an association of Down's syndrome not only with maternal exposure to fluoroscopic and therapeutic radiation but also possibly with paternal radar exposure, replication of the original study was undertaken on parents of 300 "Current Series" cases and controls born in 1962-1968 and 1945. In addition, validation of military service and radar exposure through search of government records on all Original and Current Series fathers (involving 791 cases, controls, and new matches) and a chromosome study of 162 radar exposed and unexposed fathers (159 with successful cultures) of both series were carried out. The findings in the Current Series (a) confirmed the maternal age effect and lack of an advanced paternal age effect in Down's syndrome, but, (b) in contrast to the Original Series, showed no difference in medical radiation between case and control mothers (or fathers), fewer pregnancies and somewhat more fetal loss prior to the index child in mothers of Current Series cases, and no difference in radar exposure between case and control fathers. Even when the two series were combined, no significant differences were observed between case and control fathers in radar exposure or in military service, although there appeared to be slightly more Army service in case fathers in each series and a borderline ($p<.053$) excess in Marine service of Original Series case fathers, with the opposite trend in the Current Series. A suggestion of

more chromosome aberrancy in radar exposed than unexposed fathers of the Combined Series is provocative but puzzling, in view of the type of deviants in excess (gaps and single chromatid breaks - usually considered to be due to technical error). Despite the possibility that the cytogenetic findings may indicate greater chromosome fragility associated with microwave exposure or be otherwise biologically meaningful, they may be spurious. Caution is needed in their interpretation and more definitive, preferably, longitudinal studies are required for confirmation or rejection.

FOREWORD

This report deals primarily, but not exclusively, with the parents of a series of white Down's syndrome cases and matched controls born October 1, 1962 through December 31, 1968 and anytime during 1945, referred to as the "Current Series". The Current Series constitutes the study population ascertained for a "replication" study of the initial investigation based on the "Original Series". The Original Series comprised white cases and controls born January 1946 - September 30, 1962; its basic findings were reported in publications #2 - #5 attached as Appendix B for reference purposes. Supplementary, updated, and/or unreported data on the Original Series are presented for certain pertinent aspects, including all aspects specified in the itemized scope of work of the Contractor's Proposals. Where feasible, comparisons are made with the Original Series and tabulations on the Combined Series (comprising the Original Series + the Current Series) given. All data pertaining to the validation of military service and radar exposure, and to the chromosome studies are presented for fathers of the Original Series as well as fathers of the Current Series.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

Index Child

Parental Age

Paternal Radar-Microwave and Ionizing Radiation Exposure

Paternal Radar-Microwave and Ionizing Radiation Exposure (Cont'd)

TABLE R-2	Paternal Radar Exposure before Conception of Index Child (From Interview) Current, Original, and Combined Series Matched Pairs and Pooled
TABLE R-3	Paternal Radar Exposure before Conception of Index Child (From NAS) Current, Original, and Combined Series Matched Pairs and Pooled
TABLE R-4	Paternal Radar Exposure before Conception of Index Child (From Interview and/or NAS) Current, Original, and Combined Series Matched Pairs and Pooled
TABLE R-5	Time of Paternal Radar Exposure (From Interview) Current, Original, and Combined Series Matched Pairs and Pooled
TABLE R-6	Time of Paternal Radar Exposure (From NAS) Current, Original, and Combined Series Matched Pairs and Pooled
TABLE R-7	Paternal Radar Exposure Status by Time of Radar Exposure (From Interview and NAS) Current, Original, and Combined Series Matched Pairs
TABLE R-8	Paternal Radar Exposure Status by Time of Radar Exposure (From Interview and NAS) Current, Original, and Combined Series Pooled
TABLE R-9	Paternal History of Military Service on Shipboard (From Interview) Current, Original and Combined Series
TABLE R-10	Paternal History of Work with Radar in Military Service (From Interview) Matched Pairs of Current, Original, and Combined Series Pooled Fathers of Current Series
TABLE R-11	Paternal History of Work with Microwave in Military Service (From Interview) Current, Original, and Combined Series
TABLE R-12	Paternal History of Work with Electronic Products in Military Service (From Interview) Current, Original, and Combined Series
TABLE R-13	Paternal History of Work with Radio Communications Gear in Military Service (From Interview) Current, Original, and Combined Series
TABLE R-14	Paternal History of Work Involving Special Sites and/or Equipment in Military Service (From Interview) Current, Original, and Combined Series

Paternal Radar-Microwave and Ionizing Radiation Exposure (Cont'd)

Paternal Military Service

Parental Radiation

Parental Radiation (Cont'd)

Parental Social and Economic Factors

Maternal Marital and Reproductive History

Maternal Medical and Reproductive History (Cont'd)

Maternal Medical History

Maternal Medical History (Cont'd)

Chromosome Studies: Current & Original Series Plus New Matches

LIST OF APPENDICES

INTRODUCTION

Format of Report

This final report on Contract No. DADA 17-69-9154 and Contract Nos. DAMD 17-75-M-5883 and DAMD 17-76-M-5883(amended and extended to complete the provisions of the aforementioned Contract DADA 17-69-9154) is presented in accordance with the Contractor's agreement "to conduct studies on research project entitled PARENTAL RADIATION AND DOWN'S SYNDROME (MONGOLISM), WITH PARTICULAR ATTENTION TO IONIZING RADIATION AND RADAR". For the purpose of clarity, the expanded Specific Aims and Scope of Work, as designated by the contractor in the extension proposal of 1 June 1970, provide the outline of presentation of the study findings. For reference purposes, therefore, the following are attached in Appendix A:

a. Proposal for initiation of current study submitted Spring 1969[x]

b. Proposal for extension of current study submitted Winter 1969-1970[x]

The stated purposes of "a" and "b" are:

a. As stated in the Spring 1969 proposal: "To determine whether parents of Mongols differ from parents of matched normal controls with regard to exposure to radar and/or ionizing radiation and to examine the chromosomes of those radar exposed parents and corresponding parents from matched series for any discernible differences and/or abnormalities".

---

[x] NOTE: Support of the initial study (i.e., Original Series) of "Parental Radiation and Down's Syndrome", as well as partial support for the "current study" and its ramifications, was received from the Bureau of Radiological Health.

b. As stated in the extension proposal Winter 1969-70: "To extend the investigation of (1) radar and/or ionizing radiation exposure of parents of Mongols and parents of their Matched Controls, and (2) possible chromosomal aberrations among fathers radar exposed and unexposed by including a series approximately 50% larger than originally estimated".

The Specific Aims, in addition to being attached in Appendix A, are given at the beginning of the respective sections pertaining to them.

Organization plan:
This report is organized as follows:

(i) Background and purpose of this investigation.

(ii) Method: study design, procedure, study subjects, sample ascertainment and description, definitions, criteria, and classifications, etc.

(iii) Results

a. Observations pertinent to the Specific Aims under proposed Scope of Work.

b. Fulfillment of itemized tasks under Scope of Work.

(iv) Discussion, Conclusions, and Overview

(v) Narrative: Summary of (i) through (iv) above with emphasis on most pertinent findings, including a discussion and overview.

(i.) BACKGROUND AND PURPOSE

The background and purpose of this investigation are summarized in a series of publications # 1-5.[x] A review of the epidemiological studies of Down's syndrome (mongolism), prior to and in the first years after its chromosomal basis was established[6], indicated some of the unanswered questions on Down's syndrome, providing the basis for this investigation [1]. The original investigation was designed to study, by interview technique and medical record analysis, a population of parents of white children with Down's syndrome and parents of control children for exposure to certain environmental agents or health hazards postulated to cause nondisjunction or to increase the risk of the chromosomal abnormality of Down's in their offspring through some mechanism. Included among its fundamental objectives was the examination of the possible role of the father, as well as the mother, in the pathogenesis of the defect. For this purpose, the Original Series of of 216 white Down's syndrome cases (born January 1, 1946 through September 30, 1962) and 216 controls matched on maternal age, hospital of birth, race, sex, and date of birth [2-5] was ascertained.

The findings on the role of parental age [2], radiation exposure [3], reproductive and marital history [4], as well as other pertinent epidemiological aspects of that Original Series were summarized in the Annals of the New York Academy of Sciences, September 24, 1970 [5], as follows:

a. The well documented association of Down's syndrome with maternal age was confirmed, but no association with paternal age was observed.

(x) Publications #1 through #5 are attached as Appendix B.

b. The mothers of Down's children had received significantly more radiation, particularly fluoroscopy and therapeutic radiation, than the mothers of control children. In fact, for combined radiation from one or more diagnostic, fluoroscopic and therapeutic sources, the frequency of mothers of Down's children who had undergone such procedures was seven times that of control mothers. Of additional interest was the observation that significantly more mothers of cases were employed in professional or technical occupations in the medical field. The consistency of these relationships was noteworthy.

c. Another association of interest was the higher frequency of multiple marriages among the mothers of the Down's children as compared to the controls. Although broken marriages might be expected following the birth of a defective child, they were not as easily explained when they occur before the birth. It seemed possible, however, that in a study in which a great many factors are examined, one or more chance associations would appear. Whether this multiple marriage association was a chance finding remained to be determined.

d. With respect to pregnancy wastage, fertility, and menstrual irregularities, the mothers of the Down's children did not differ from the control mothers nor did they show a higher frequency of other offspring with congenital abnormalities.

e. The radiation history of the fathers provided a contrast to that of the mothers. There was a marked similarity in the history of radiation exposure reported by the fathers of Down's and of controls, except for the suggested relationship between Down's syndrome and paternal radar exposure. Although it seemed possible that this finding

was a chance observation due to the small numbers available, this suggested relationship appeared worthy of additional investigation.

The voluminous literature concerning postulated etiological factors in Down's syndrome that had preceded the recognition of the chromosomal basis of Down's Syndrome(6) and continued to accumulate after 1959 did not clarify the agents or mechanisms responsible for the chromosomal defect nor provide an insight into the observations "a" through "e" above. (See Table 1.)

In view of the need to confirm the positive findings, the original Hopkins study was extended, beginning in June 1969, to include additional Down's syndrome children [x] born from October 1962 through December 1968. The latter extension is essentially an independent replication of the previous study. The current study also added two other features: (1) a validation of military service and radar exposure, and (2) a chromosome study of radar-exposed fathers and unexposed fathers [⊗] of matched controls. Finally, in June 1970 the study was extended further to include a larger sample, when it became apparent that more cases could be ascertained than originally estimated.

Because of the increased number of sources of ascertainment, as well as more sensitive diagnostic procedures and case finding techniques among physicians, private and public agencies, and possibly also improved searching techniques, it was possible, to obtain a larger study series than previously anticipated: 150 white cases and 150 controls rather than the 95 of each previously estimated were ascertained,

---

[x] Appendix C-1 contains Criteria for classification of Down's syndrome in the Current Series.

[⊗] Appendix C-2 contains Radar exposure categories of fathers.

yielding 128 matched pairs of confirmed cases and matched controls. The remaining 22 cases included additional or unmatched cases and a few questionable cases. The additional 22 controls were unmatched controls. On the tabulations presented for comparison of Down's and controls and/or parents of cases and controls, it is specified, as to whether "matched pairs" are being considered or pooled cases and pooled controls - the "pooled"including the additional, questionable, and unmatched.

With regard to the chromosome studies, in the previously published [3] series, 18 fathers of children with Down's syndrome and seven fathers of control children reported definite radar exposure with several additional fathers having probable or questionable exposure. Thus 25 to 33 fathers and the 25 to 33 fathers of children matched to those cases and controls from the Original Series were to be located and blood drawn for chromosome analysis.

It was then estimated that the Current Series (based on study of 95 cases born October 1, 1962 to January 1, 1969 and 1945 in the Baltimore area) would yield at least 11 additional exposed fathers and 11 matched unexposed fathers, making a total of 72-80 fathers on whom chromosome studies would be carried out. That estimate assumed that the rate of Down's syndrome, ascertainment, and radar exposure would be similar for the years to be studied to those years already studied. With the subsequent recognition that a larger Current Series would be available and including those who had worked "near" radar, the estimate was revised to 60 to 70 fathers "radar exposed". Thus, with the matched unexposed fathers, the estimated number of persons on whom chromosome studies would be performed increased to approximately 120 to 140. With deaths

and refusals, a conservative estimate of 110 to 120 was considered plausibie. (See Appendix A). In the final sample there were 162 fathers with chromosome studies: 55 matched pairs of 55 exposed and 55 matched unexposed fathers, 7 matched pairs of 7 near exposed and 7 matched unexposed fathers, and 38 unmatched fathers (26 exposed and 12 unexposed). The derivation of these subjects for the Chromosome Study is discussed further below under Methods and Results. NOTE: No attempt was made to determine directly whether radar caused damage to the germ cells; instead the objective of this study was to examine possible microwave associated effects on somatic cell chromosomes (of the peripheral blood) as an indirect indicator of likelihood of deleterious effects on chromosomes of the germ cells as well as persisting effects on somatic chromosomes.

In this report, the data derived from the original study of Down's children are referred to as the "Original Series" (born January 1, 1946 - September 30, 1962), and those from the replication study (born October 1, 1962 - December 31, 1968), referred to as the "Current Series". It should be noted however, that a few Down's cases who had been born in the "Original Series" time period were ascertained with the Current Series; and, as they had not been in the previous series, they were included for study in the Current Series along with their matched controls. Also, the Current Series ascertained as many Down's syndrome cases born in 1945 as available, along with matched controls for them, in order to complete, insofar as possible, the study series encompassing the years 1945 through 1968.

As noted above, publications pertaining to the Original Series and its background (references 1 through 5) are attached in Appendix B, both to provide the background of the current investigation and for reference purposes (since many of the same tabulations have been carried out for

the "Current Series"). Consequently, the original findings will not be reviewed in detail here nor will the tables be presented again, except where there are supplementary, updated, or different types of tabulations.

(ii) METHOD

The design of the overall investigation is outlined below, and the specific methods of procedure considered.

STUDY DESIGN:

As shown in Figure 1, the overall plan of the investigation consists of two main aspects:

I. Role of parental factors in Down's syndrome: in particular, radiation exposure, but also other factors

II. Chromosome studies of radar exposed and unexposed fathers

The first aspect of this investigation (I. Role of parental factors) encompasses both the original study, which involved the Original Series Down's cases and controls born through September 1962, the findings of which have been reported [2-5] and the subsequent or "current" study, which included the following:
(a) ascertainment of the Current Series born October 1962 through December 1968, and collection of information on parents, index children, etc., on this series similar to that obtained for the Original Series, in order to enlarge the sample and to replicate the original study; (b) collection of supplementary information concerning possible exposure to radar and/or other sources of microwave in the Current Series, as well as follow up on the fathers in the Original Series for similar information; and (c) validation of military service and radar exposure insofar as possible by arrangement with the National Academy of Sciences (NAS) to carry out an independent "blind" (x)

(x) "Blind" - The list submitted to NAS did not allow identification of case-control status of subjects; therefore, searchers did not have this information when searching for records or recording observations.

search on all fathers in the study (both Original Series and Current Series) to obtain information on their military service, if any, (including length of time and date of service, and military occupational classifications) to determine likelihood of radar exposure.

The second aspect (II. The Chromosome Studies) involved examining the chromosomes of radar exposed and unexposed fathers of Down's cases, of controls, and of "new matches" from both the Original and Current Series.

The initiation point of study in the Original Series was ascertainment of the index case with Down's syndrome. To each Down's index case, a control child of the same sex and race born in the same hospital, to a mother of the same age, at the nearest date, was matched by birth certificate. Thus, the ascertained white Down's syndrome cases plus the controls matched to them comprised the index children. The parents of the index cases and controls thus became part of the study sample and, in fact, the main study individuals. A similar procedure was used for the Current Series.

As shown in Figure 1, the Original Series involved the parents of Down's cases born January 1946 through September 1962 and the parents of their matched controls: as reported, the parents of 216 Down's cases and of 216 matched controls.[2-5] The Current Series involved Down's cases born October 1962 through December 31, 1968, plus as many Down's cases born in 1945 as could be ascertained and whose parents were available for interview, as well as a few children born in the time period of the Original Series, but not ascertained until the Current Series was obtained. Along with these Current Series cases were the controls matched to them.

While certain basic information concerning the index cases of Down's and their controls has been collected, the main orientation of data collection and analysis pertains to parental factors. For Aspect I, the data are primarily from the interview of case and control parents and the NAS search of military records, with some data derived from medical records and other sources.

In the second aspect of the investigation (II. The Chromosome Studies) as shown in Figure 1, comparisons were made between chromosomes of radar exposed and unexposed fathers irrespective of whether they were fathers of cases, controls, or new matches. The "unexposed" comprised fathers for whom, from interview and NAS search, there was no evidence of any exposure to radar other than whatever exposure is found in the general population . The basic plan was to study (1) radar exposed fathers of Down's cases vs. fathers of their matched controls, provided the latter were unexposed; and (2) radar exposed fathers of matched controls versus fathers of the Down's cases to which they were matched, provided the latter were unexposed. However, additional fathers, designated "new matches", had to be obtained to complete the study design where "an unexposed father" was not available from the "matched pair" yielding the exposed father . "New matches" were also required where both fathers in a matched pair were "exposed" or where the father matched to the exposed father was deceased, living out of the area, not located, or unable, or unwilling to participate. As a result, five different derivation combinations of "exposed" and "unexposed" fathers were used for "matched pair" comparisons in the Chromosome Studies, as shown in Figure 1. The distribution, total numbers, method of ascertainment and other factors concerning those combinations

are discussed further in the "Method of Procedure", "Results", and other following sections where pertinent.

METHOD OF PROCEDURE:

The specific method of procedure for case selection, control matching, interview, and record data collection followed in the original study is described in the publications # 2-5 found in Appendix B. For the Current Series, the procedure for subject ascertainment and interview was essentially similar to that followed in the original study, with minor adjustments related to differences in facilities, time period, etc.

STUDY SUBJECTS:

Index children:

Ascertainment of index cases of Down's syndrome for the Current Series involved multiple sources, as for the Original Series [3]. The sources of ascertainment included the following:

Health Department - Baltimore City
- Handicapped Children
- Department of Biostatistics (Birth Certificates)

Baltimore Association for Retarded Children

Schools and Training Centers
- Battle Monument
- Chimes Activity
- Claremont
- Ridge
- Rolling Road
- Rosewood
- St. Francis
- Searchlight

Hospitals
- Baltimore City
- Bon Secours
- Church Home
- Franklin Square
- Greater Baltimore Medical Center
- Johns Hopkins
- Lutheran
- Maryland General
- Mercy
- St. Agnes
- St. Joseph's
- Sinai
- South Baltimore General
- Union Memorial
- University of Maryland

Children with a diagnosis of Down's syndrome meeting the criteria described below and in Appendix C and born in the greater Baltimore area between 1/1/45 and 12/31/45 and also those born 10/1/62 through 12/31/68 were included, plus a few born in the Original Series time period but not ascertained therein.

Index Case Documentation:

Objective criteria were established for verification of a diagnosis of each presumptive Down's case as a case eligible for inclusion in the study series. The criteria for the Original Series have been described (p. 633-4, J. Pediatrics 1965 [2]). For the Current Series, only a few minor modifications were necessary. The diagnostic criteria for case eligibility in the Current Series were as follows: 5 or more stigmata indicated on hospital or physician's records from among the following: chromosomal evidence, brachycephaly, slanted palpebral fissures, epicanthic folds, palmar simian lines, malformed ears, broad and/or short neck, malformed fingers and/or hands, nasal abnormality, hypertelorism, abnormal palate, furrowed tongue, abnormal handprints and/or footprints, Brushfield spots, abnormal hip angles, broad and/or short trunk, congenital heart condition. (See Appendix C-1)

Exceptions to the requisite of 5 stigmata for elgibility as cases included: 1) A deceased child with 3 stigmata documented plus mention of mongolism (or Down's, etc.) on death certificate, or on hospital record, or with physician's confirmation; 2) A living child with fewer than 5 stigmata listed on records but with chromosome studies done and Trisomy 21 confirmed.

The physical characteristics (stigmata) in Down's syndrome cases of the Current Series are tabulated for both matched cases and pooled cases (Table B-1). For cases from the matched pairs, documented physical findings include: brachycephaly (>47%), slanted palpebral fissures (>73%), epicanthic folds (>77%), simian lines (>67%), malformed ears (>55%), broad and/or short neck (>40%), hand malformations (>70%), hypertelorism (>23%), abnormal palate (>44%), furrowed tongue (>61%), Brushfield spots (>39%), hip abnormalities (>11%), broad-short trunk (>12%), and congenital heart condition (>46%). For total cases in the pooled group of 150, 128 or 85.3% of which are matched pairs, the distribution of stigmata is very similar. As expected, the "questionables" had fewer stigmata, while the "additional" mongols do not differ markedly from matched pair cases, as their status is due, in most instances, to failure to obtain either parental data or an appropriate matched control, rather than failure to meet criteria.

Table B-2R gives the distribution of number of stigmata for cases in matched pairs. For those 11 with fewer than 5 stigmata, the subjects are listed: 7 were deceased and had the requisite 3+ (5 had 3 and 2 had 4 stigmata each); 2 of the living were chromosomally documented as Down's syndrome, while the 2 others each had 4 stigmata plus a physician's confirmation in one case, and two hospital records and a birth certificate noting "mongol" in the other.

Selection of control subjects: As in the Original Series, birth certificates of the children with Down's syndrome in the Current Series were located, and their place of birth and other vital information verified. Control subjects were selected by rigidly matching, in a systematic manner, each case with another certificate for (1) hospital

of birth (or at home), (2) sex and race of child, (3) maternal age at time of birth of child and (4) date of birth.

In each case the "best control" was a child whose birth date was closest to that of the Down's child of the same sex, born in the same hospital to a mother of the same age. If the "best control" on the basis of established criteria either had left the state or could not be located, the next best control was selected (e.g., with slightly greater difference in birth dates), the other criteria remaining the same.

The hospital records as well as birth certificates of all control children were examined to be certain that the "normal" control group contains no cases of Down's syndrome.

The final composition of the study groups of index children (cases and controls) for the Current Series and Original Series, as well as the New Matches is given in Table B-3. The Current Series comprised 128 matched pairs (128 Down's cases and 128 controls matched to them) plus 13 additional cases and 9 questionable cases as well as 22 additional controls thus yielding 150 "pooled cases" and 150 "pooled controls". Parental factors were studied similarly but tabulated separately for comparisons involving the matched pairs and for those of the pooled groups, respectively.

In the Original Series, the reported comparisons of parental factors [2-5] in Down's cases and controls were limited to the 216 matched pairs only (216 Down's cases and 216 matched controls). The fathers of an additional 6 cases and 5 controls have been included in the chromosome study, although they were not included in the original study. "New

Match" children were ascertained for completing comparison sets of fathers in the chromosome study only. In total there were 37 new matches for the Original Series and 11 for the Current Series. Because some of the fathers of these "New Matches" were later found to have been radar exposed and/or because of later unavailability of their match or ineligibility, of either, etc., some of the "New Match" fathers were also ultimately "unmatched".

Parents of cases and controls:

Whereas the index children provide the initiation point for study, parents are the principal subjects being studied.

The parental age distributions for Down's cases and controls of the Original Series have been described [2]. The Current Series shows patterns similar to the Original. The results of matching on maternal age, are indicated by the almost identical maternal age distributions for cases and controls. Matched pairs are shown in Table A-1; pooled, including the unmatched cases and controls respectively, are shown in Table A-2; and comparison with total Baltimore City live births and state of Maryland live births for the specified time period, in Table A-3. In the matched pairs, 4.7% of case, and the same percentage of control mothers were under 20, with 18.0% of case mothers and 18.8% of control mothers respectively over 40 years of age. When compared with total Baltimore City live births and Maryland state live births, the age distribution of mothers of cases (and consequently that of mothers of controls matched on maternal age) appears markedly shifted to the older age groups, as shown in Figure A-1, thus indicating the clear maternal age association observed in other studies of Down's syndrome.

Doubtless, as a consequence of both the correlation of husbands' ages with that of their wives and of the age-matching of case and control mothers, the age distributions of case and control fathers were also considerably shifted to the older groups as compared to the fathers of all white children born during the same time period in Baltimore City.

It is of interest, however, that given case and control fathers whose spouses were age-matched and who were consequently also similar in age distribution, whatever age difference, if any, appears between them tends toward a negative association with Down's. That is, Current Series, like Original Series, case fathers tend to be younger than control fathers; in fact the difference attains statistical significance ($p < .05$) in the Current Series. Somewhat fewer control fathers than case fathers were under 24 and more were over 40, including some over 50. (30.5% of case fathers as compared to 36.7% of control fathers were over 40.) Thus, the absence of an association of advanced paternal age with Down's, noted in the Original Series [2], was confirmed.

In addition to age, various sociobiological characteristics of parents were examined. These are discussed below with Specific Aim 3, constituting part of the "Results" section.

Data collected:

While some of the information collected pertained to the index children, the major portion of the data involved the parents of the index cases and controls.

Records: Birth records (certificate and hospital) and other available hospital and medical records on parents and children were examined for pertinent information, as well as paternal military

service records discussed below.

<u>Interviews</u>: The interview data collected on the <u>Current Series</u> were of the same type as on the Original Series, except that some supplementary detailed questions concerning experience with radar, microwave, and military service were added. In addition, the fathers from the Original Series were recontacted and given a short form follow up interview with regard to those supplementary data. (See <u>Appendix D</u>.) In some cases where fathers were not available, their spouses provided the necessary information. As in the Original Series, Current Series mothers and fathers were individually interviewed to obtain the required information. Where mothers or fathers were deceased, information was obtained insofar as possible from the surviving parent. Where both parents were deceased, the subject was excluded from the matched series, although included in the pooled group, if sufficient data were available.

Interview data in the Current Series interview include:

1. Complete names and addresses of each parent, index child and sibs.

2. Child's sex, place of birth, physician, and history of hospitalizations and medical conditions.

3. Mothers' education; religion; and histories of residence, occupation, and marriage; medical data including: histories of illnesses; menstruation, pregnancy, hospitalization and details of radiation exposure insofar as possible - diagnostic X-ray, radiation therapy, fluoroscopy, and injection or ingestion of radioactive substances.

4. Fathers' education; religion; residence; occupational history with detailed information about military service; marital history; number of offspring; illnesses; medical and hospitalization histories; etc.

5. Other pertinent epidemiologic, demographic, and sociobiological data.

The mother and father were usually interviewed independently at home. The approach to both the families of the mongols and controls was uniform. The interviewers were not informed which were cases and controls and could not make the distinction between families until the actual interview was conducted, if then. Questions about radar and radiation exposure, medical conditions, and occupation were phrased without reference to the birth of the index child. Insofar as possible, dates of exposure were obtained, however, so that the time-relationships relative to the index child could be examined in the analysis.

Validation of findings derived from interview data was attempted by independent and simultaneous examination of several characteristics of the parents of mongols and of controls as well as through independent search of medical, military and other records.

Validation of Military Service and Radar-Microwave Exposure: Validation procedures for military service/radar exposure include the independent ascertainment of data through search of military files on all fathers, irrespective of whether they reported such service/exposure or not. In addition to responses to questions regarding radar and microwave exposure incorporated in the Current Series interview and a follow-up interview of the Original Series using the same questions, to obtain objective information on military service, radar exposure, etc., an independent search of U.S. Government military service records was also carried out.

An arrangement was made with the National Academy of Sciences (NAS) Follow Up Agency to perform the search of military service records and occupational classifications at the National Personnel Record Center - Military Records - in St. Louis, Missouri. A list of the names of all fathers of cases, of controls, of new matches, etc., (irrespective of whether any service history was known) was submitted to NAS without identification of case-control status or interview responses on exposure. Therefore, searchers did not have this prior information when looking for records or reporting observations. Classification of military jobs, e.g., MOS (Military Occupational Specialty), numbers and job titles, with regard to exposure was determined independently by Army and Navy consultants.

Definition of what constituted exposure to radar, and thus classification of fathers as "exposed" or "unexposed" turned out to be complicated, even after consultation. Therefore, separate tabulations are presented for the findings from interview only, from NAS search only, and from the combined data. Categorizations for each differs slightly because of the variation in types of information available. In the classification based on interview report only, i.e., where subjects are categorized on the basis of response to interview questions), a subgroup that reported having been "near" radar or radar installations but not having worked "with" radar was classified as "near exposure". Another categorization was based on NAS report of military jobs held and the classification of those military jobs with regard to exposure, as determined by Army and Navy consultants. Still another categorization

was based on combined information from NAS and interview.

These are described further with the discussion of the respective tabulation in the Results section below. The criteria for the classifications of radar exposure are listed in Appendix C-2, as previously indicated above.

The radar exposure categorization of fathers in the Chromosome Study was based on a combination of interview responses, military service records and consultants' classification of MOS and job titles. Three classes were used "exposed," "near exposure," (e.g., for fathers who worked near radar equipment but not with it) and "unexposed".

Chromosome Studies

Subjects in the Chromosome Study:

For the "chromosome study", all fathers of Original and Current Series subjects "exposed" to radar (according to established criteria of "exposure" [x]) and available for study, and "unexposed" fathers matched to them (through the established criteria for matching of index children) and available for study were included. As indicated above, the basic plan was to examine and compare the chromosomes of (1) radar exposed fathers of Down's cases and the unexposed fathers of their matched controls and (2) radar exposed fathers of controls and the unexposed fathers of the cases to whom they were matched. Only a limited number of such combinations were available, however, necessitating the use of "new matches".

For example, if the fathers of controls in (1), or Down's cases in (2), were exposed or unavailable for study, the index child of the exposed father was matched by sex, race, hospital of birth, maternal

[x] See Appendix C.

age, etc. (i.e. by all the criteria used for the original matched pairs) and the father derived from the resultant match became a "new match". Thus the new-matched fathers were ascertained for a comparison series and were matched either to exposed fathers of Down's cases or exposed fathers of controls. To be eligible, however, the "new matched" father also had to have been unexposed to radar and therefore was subjected to the screening interview. In those cases where the new match turned out to have been exposed, another new match was identified; new matches were sequentially selected until an unexposed "new match" available for study was obtained. Wherever possible, "exposed" new matches were also included in the study. A "new match" pair was derived if an unexposed new match could be obtained for a comparison. Thus there are the 5 matched pair comparison combinations for chromosome studies as indicated in Figure 1.

These include:

(1) Exposed Down's fathers vs. Unexposed Control fathers

(2) Exposed Control fathers vs. Unexposed Down's fathers

(3) Exposed Down's fathers vs. Unexposed New Matches

(4) Exposed Control fathers vs. Unexposed New Matches

(5) Exposed New Matches fathers vs. Unexposed New Matches

Separating "exposed" into "definitely exposed" and "near exposure" classes, there are, in fact, 10 different types of matched pairs, although none of the pairs on which chromosome studies were done were in the last category (i.e. new match fathers near exposure with unexposed new matches, (See Table CS-1).

An attempt to obtain blood samples, culture chromosomes and complete chromosome analyses on all such eligibles were made. There

were, nevertheless, several problems.

As noted above, definition of what activities and/or locations constituted exposure to radar, and thus the complexity of classification of fathers as "exposed" or "unexposed" even after consultation necessitated the use of multiple sets of categorizations, and the derivation of a combined categorization for the Chromosome Study.

Besides exposure classification, another difficulty was that not all fathers were available for study - e.g., some were deceased, lived out of the area, refused, could not be located, or were unavailable for other reasons. Finally, of those available and classified, some had unsatisfactory blood samples, chromosome cultures that failed to grow, or other technical problems. Wherever possible, resampling was done if the problems were only technical and fathers were still available for study.

Method of Chromosome Analysis:

Chromosome culture: Samples of venous blood were obtained from available eligible "exposed" and unexposed fathers in vacutainers.

The whole blood culture technique was followed. Lymphocytes were stimulated to grow *in vitro* in the presence of phytohemagglutinin for about 69 hours at 37.4°C. Colchicine was added for 2 1/2 hours (0.025 to 0.03 ml of 20 ug/ml). Cells were treated with a hypotonic solution of Sodium Citrate (0.7%) for 20 minutes at 37.4°C. The cells were then fixed in 3:1 absolute alcohol: glacial acetic acid. After one change of this freshly prepared fixative they were refrigerated overnight to a period of two days. Microscope slides were prepared after three changes of fixative. The cells were splashed on to the ice cold water-wetted slides from a length of about 12-18" and blown by mouth. They were stained with Giemsa stain and analyzed.

Microscopic study: Search for analyzable metaphases was first conducted with a 10X objective. When suitable metaphase plates were ascertained, a detailed chromosome analysis was done with a 90X oil immersion objective. Very infrequently metaphases were rejected at this stage for inclusion in the final count; and then only because there was small number of chromosomes, i.e., broken cells, overlapping of chromosomes, fuzzy appearance, insufficient staining, etc. As a quality control measure, a number of abnormalities were reexamined by another investigator. The observers and all the laboratory staff had no knowledge of the radiation exposure status of the subjects when conducting their examinations.

(iii) RESULTS

The findings are presented in terms of: the specific aims and the scope of work indicated in the project plan of the Contractor's Proposal submitted Winter-Spring 1969-1970.

It is stated in the Contractor's Proposal for the extension of the project that the Specific Aims would remain the same as previously specified but were to encompass investigation of approximately 140 or more cases of Down's syndrome and an equal number of families of control subjects, instead of the original estimate of 95 cases and 95 controls. As discussed above and indicated in Table B-3, the Current Series did encompass 150 cases and 150 controls in the pooled group which includes 128 matched pairs including 128 documented Down's cases and 128 controls matched to them. The Down's cases in the matched pairs comprise only definite cases meeting the established criteria. The comparisons presented in the tabulations and discussed in the text are concerned primarily with the matched pairs, although some data are presented on pooled groups as well. It should be noted that many unmatched cases (i.e., those listed as additional cases) meet all the necessary criteria but might have failed to become a member of a matched pair because no appropriate control child could be matched within a reasonable time period or because one of the parents of a case or control refused, could not be located, etc.

OBSERVATIONS PERTINENT TO SPECIFIC AIMS

SPECIFIC AIM 1

1. To compare the parents of mongols with those of controls with regard to reported radar exposure, occupations involving radar exposure, or exposure to any occupational or military sources of radioactive substances or radiation.

Radar-Microwave Exposure (and other Radiation) from Military or Occupational Activities

Below is a summary of the findings based on (1) the incorporation of more detailed questions regarding radar and microwave exposure in the Current Series interview and a follow-up interview of the Original Series using the same questions, plus (2) the search of military service records by NAS[x], with classification by Army and Navy consultants of military job titles as to exposure.

Radar exposure reported on interview was classified as follows: a) no evidence of exposure prior to conception of index child indicated in any of the responses to interview queries; b) probably no exposure - some equivocal response but no real exposure likely other than that received by the general population; c) probably some exposure - exposure likely in excess of that received by the community in general: e.g., worked in industry where radar was used, mobile radar in his unit, radar on his ship, stationed at a radar park, etc; and d) exposed - occupation or service definitely involving radar / microwave operations, thus likely in excess of general population exposure.

x As already noted, to obtain objective information on military service, radar exposure, etc., names of all fathers were searched for past military history and all occupational classifications, via an arrangement made with NAS to perform this search. No identification as to whether name belonged to a father of mongol, control, new match, etc. was given when the list of names was submitted to NAS.

Table R-1 summarizes, from interview data only, the radar-microwave exposure history of fathers of cases and controls in matched pairs and pooled groups (including unmatched fathers). Time relative to conception is not considered in this tabulation; thus, the exposed fathers whose exposure may not have been prior to the conception of the index child are included. Limited to matched pairs only, a smaller percentage of case than control fathers reported some type of exposure in the Current Series (17.3% vs. 21.3%), a larger percentage in the Original Series (22.6% vs. 16.1%), with the counterbalanced effect in the Combined Series (20.5% vs. 18.1%) observed. Including those with"probably some exposure"(27.5% vs. 29.2% in the Current, 25.2% vs. 16.6% in the Original, and 26.1% vs. 21.4% in the Combined Series), the excess in case fathers clearly derives from the Original Series, as was the pattern using only the "Exposed".

Tables R-2, R-3, and R-4 contain data as to whether fathers had any radar exposure before conception of the index child irrespective of whether such exposure extended into the period following conception or not.[x]

Table R-2 summarizes, from interview data, paternal radar exposure reported to have occurred prior to conception of the index child,[x] classifying exposure in categories of "no exposure","probably some exposure",and "exposed". As observed in Table R-1 (which disregarded time relative to conception of index) and in contrast to the Original Series,

[x] NOTE: In all tabulations of radar exposure, military service, etc., where time relative to the conception of the index child is indicated, priority is given to "time" before or "prior" to conception of the index. Therefore, if exposure extended over a period of time which overlapped, encompassed or included any time prior to index conception, even if the proportion of the prior exposure was very small relative to the total exposure, the exposure is, nevertheless, coded as "Prior".

Table R-2 shows Current Series control fathers to have rates of definite exposure (omitting "probably some") almost 50% higher than case fathers (but NSD): 8.3% in case fathers vs. 12.6% of control fathers from matched pairs (p = .61). Combining the "probably some" with those definitely exposed (21.6% vs. 23.5% for matched pairs), the trend is still in the opposite direction from that of the Original Series. While the reevaluated Original Series continues to show an excess of case fathers reporting exposure (13.8% versus 11.5% for matched pair control fathers), the difference is not significant and the margin is narrower than previously assumed from initial review. Adding in the "probably some" group gives 18.6% of matched pair case fathers exposed as compared to 13.4% of control fathers (p = .27). When the Original Series is combined with the Current Series, the differences previously reported are counterbalanced and all but disappear: for those with definite exposure 11.5% case fathers vs. 12.0% control fathers of matched pairs; and when including those with "some exposure": 19.8% vs. 17.8% (p = .62).

Table R-3 deals with paternal radar exposure before conception of the index child, utilizing NAS information only and using only two categories of exposure "Not exposed" and "Exposed". Here where the categories are limited to exposed, not exposed, and unknown, the patterns remain the same as those in the interview data. In the Current Series, evidence for radar exposure was documented in 8.8% of case fathers and 11.9% of control fathers when limited to matched pairs only; in the Original Series, 10.3% vs. 8.2% for case and control fathers respectively in the matched pairs. Thus, as with the interview data, the slight deviations of the two series in opposite directions tend to counterbalance

and the Combined Series yields almost identical exposure rates for case and control fathers of matched pairs (9.8% vs. 9.6%).

Table R-4 summarizes paternal radar exposure before conception of index child from combined interview and/or NAS, recording exposure in terms of probability of exposure prior to the conception of the index child in the following categories: "No exposure definitely prior"; "Probably no exposure", "Probably some exposure", and "Exposed". For Current Series matched pairs, exactly the same percentage of case and control fathers (71.7%) showed "no exposure" in the period definitely prior to conception of the index child, although a somewhat smaller proportion of case than control fathers (15.7% vs. 21.3%) appear definitely to have been exposed. If the exposed are combined with those probably having some exposure, the difference is not so marked (25.9% vs. 28.4%). In the Original Series, the deviation was consistently (though not markedly) in the opposite direction: exposed (19.6% vs. 15.7%), including probables, 21.7% vs. 16.2%; with those having definitely none prior to conception also deviating slightly (78.4% vs. 83.8%). As a result, there was counterbalancing in the Combined Series, with the larger Original Series tipping that balance only when probables were included or when those with definitely no exposure prior to the conception of index were considered. For the simple, definitely "exposed" category the frequency among case fathers (18.1%) was almost identical to that for control fathers (17.8%). None of these differences was statistically significant.

Table R-5 presents history of paternal radar exposure as reported on interview, with exposure tabulated relative to probable date of conception of the index child, including not only "before" conception but

also "during" year of conception, and "after" conception. For this tabulation, degree and type of exposure are disregarded. Those with "definite" and "probably" some exposure are considered "exposed". For matched pairs, 18.3% of case fathers, as compared to 21.0% of control fathers reported exposure before the conception of the index, and 21.6% vs. 23.5%, including those whose exposure was not only before, but also after. This is in contrast to Original Series matched pairs: 18.6% for case fathers vs. 12.8% for control fathers. The two series result in a counterbalancing effect, more markedly influenced by the larger Original,to yield, for the Combined Series, 19.8% vs. 17.4% for matched pairs and 19.4% vs. 17.9% for pooled case fathers vs. pooled control fathers for preconception exposures. Very little occurred in the post conception period.

It should be noted that there are a few differences between the sum of "before", "before, during, after" and "before and after" tabulated here and the "before" in Table R-4, even though the latter refers to all time combinations that include "before". Table R-4 includes NAS reporting in addition to interview information; and, therefore, more individuals might be listed as having exposure from the two sources. Thus, the sum of "before", "before, during, after" and "before and after", of Table R-5 yields smaller numbers than "exposed" plus "probably some" of R-4; although not smaller than the "exposed" only of Table R-4, as the "before" category of R-4 includes some individuals who, on interview, claim exposure, but who, on the basis of further NAS data, may have been classified as "probably" rather than definitely "exposed".

Table R-6 describes time of radar exposure of fathers (time relative to conception of index child) using NAS information only.

For the Combined Series, Matched Pairs, the percentage of Combined Series case and control fathers for whom there is no evidence of exposure is similar whether based on percentage known (90.2% vs. 90.5%), or total (83.1% vs. 82.6%). There are a few more unknowns among case than control fathers in the Current Series (14 vs. 10 fathers) and the opposite in the Original Series (13 vs. 20 fathers classified as unknown from NAS data). The reported exposure is low and the differences are small throughout, however, even for exposure in the specifically "before" conception category (8.8% vs. 11.9% for Current, 9.9% vs. 8.2% for Original, resulting in 9.5% vs. 9.6% for the Combined Series).

In comparing the data from interview only (Table R-5) and NAS only (Table R-6), it is not unexpected that interview reporting would yield a higher frequency of exposure as it includes non-military sources. The possibility of over-reporting of military exposure and/or reporting of military sources not documented or discernible from military records must also be considered. As for the proportion of fathers classified as unknown, it is also not surprising that the proportion is by far the highest for the data based on interview only for the Original Series (from Table R-5, 22.7% for case and 27.8% for control fathers) as recall would be more difficult with the longer time interval involved for follow up interview of that series. Accordingly, it is not inconsistent that for NAS reporting from record search (not depending on individual memory and reporting) there is no real difference between the Current and Original Series frequency

of unknowns (from Table R-6: 10.9% and 7.8% for case and control fathers respectively in the Current Series; as compared to 6.0% and 9.3% respectively in the Original Series).

Tables R-7 and R-8 give numerical cross tabulations of graded likelihood of paternal radar exposure by the time of that exposure relative to conception of the index child. Table R-7 pertains to fathers of matched pairs and R-8 to fathers of pooled (including unmatched) index children. Both tables use combined interview and NAS information. As shown in Table R-7, from the 128 Current Series matched pairs with only 1 unknown among case fathers and 1 among control fathers, 33 of the 35 case fathers with definite or probable exposure had at least some exposure prior to the birth of the index child, as compared to 36 control fathers with exposure, all of whom had some prior to conception of the index. In the Original Series, there were 21 case fathers and 11 control fathers whose exposure status was unknown. Of the 48 case fathers with definite or probable exposure, at least 42 had some prior to conception; of the 34 probably exposed control fathers, 32 had some prior to conception. Thus, the excess in the case fathers of the Original Series is apparent in the Combined Series tabulation, in which 75 of the 83 probably and definitely exposed case fathers and 68 of the 70 probably and definitely exposed control fathers had some exposure prior to conception of the index child.

As shown in Table R-8, among 150 Current Series pooled case and control fathers, 2 of 150 case fathers and 7 of 150 control fathers were unknown as to exposure status. Of the 39 case fathers with definite or probable exposure, all but 2 had some exposure before conception of index; of 39 control fathers exposed, all had some of their exposure prior to index conception.

In the Original Series, of 50 exposed or probably exposed case fathers, 42 were exposed prior; of 37 control fathers of the same exposure types, 34 were exposed prior. Thus the excess of case fathers exposed shown in the Combined Series derives entirely from the Original Series when pooled groups are tabulated, as well as when matched pairs only were considered in Table R-7.

Table R-9 tabulates interview responses regarding fathers' service on shipboard relative to time of conception of the index child. Although there was no difference in the Original Series matched pairs, for the Current Series matched pair and pooled fathers respectively, there was a very slight, but consistently higher, frequency of case fathers than control fathers who reported having served below deck prior to conception of the index child; thus for Combined Series, 5.4% vs. 4.2%. On the other hand, slightly but consistently fewer case than control fathers reported shipboard service above deck: for Combined Series matched pairs, 10% of case fathers versus 13.6% of control fathers.

Table R-10 summarizes interview responses concerning paternal work (by type) with radar in the military service relative to time of conception of the index child. For all categories of radar contact (repair, maintain, operate and test), except for "other" unspecified operations, there was a lower frequency of case fathers than control

fathers in the Current Series matched pairs, but a higher frequency of case than control fathers in the Original Series matched pairs reporting such activities prior to the conception of the index child. As a result, the Combined Series showed an intermediate pattern, taking the direction of the larger Original Series,except for the category of "operating radar", where 4.6% of case fathers vs. 5.4% of control fathers from the matched pairs reported having done that type of work. A marked deviation in the same direction was observed among Current Series pooled as well as matched fathers. Also, for other operations the magnitude as well as the pattern of difference was similar for Current Series matched pairs and pooled fathers.

Table R-11, in the same tabulation format as R-10, pertains to responses to questions indicating "microwave" rather than "radar". The frequencies of affirmative reports are extremely low for both the Current and the Original Series, with only the latter showing a consistently higher frequency among matched pair case fathers than control fathers occurring prior to index conception, thus yielding a similar pattern in the Combined Series matched pairs. With a large proportion of the comparison cells (all of those for control fathers) containing fewer than 5 individuals, it is clearly inappropriate to extrapolate as to any implications.

Table R-12 deals with paternal work with unspecified electronic products in military service based on interview data and using the same format as R-10 and R-11. The pattern of findings is similar to those of Tables R-10 and R-11. For all aspects of this type of work prior to conception of the index child, there were higher frequencies among matched pair control than case fathers in the Current Series

(except for "other" work) ; and the Original Series showed higher frequencies in case than control fathers. The pattern of the Original Series is reflected in the Combined Series matched pairs for repair, maintain and other work, but not for operating and testing electronic products in which more control than case fathers were involved in the Combined Series as in the Current Series. The tabulation for pooled fathers of the Current Series reflects the pattern of the matched pairs of that series, except for "repairing" electronic products, for which the case and control fathers showed identical frequencies.

Table R-13 is based on interview responses to questions concerning fathers' work with radio communications gear relative to time of index conception, again in the same format as the preceding tables. For both the Current and Original Series matched pairs there was a larger percentage of case fathers than control fathers who reported having repaired, maintained, operated or tested such equipment. Although the overall frequencies were low, nevertheless, there was over a twofold difference in the Combined Series matched pairs for repairing (6.6% for case fathers vs. 3.2% for control fathers), maintaining (8.1% vs. 3.5%) and testing (4.4% vs. 2.1%), with 12.1% vs. 8.1% reported for operating and no difference (1.1% for case and control fathers) in other work with radio communications gear. Current Series pooled fathers showed the same pattern.

Table R-14 compares case and control fathers with regard to history of work at special sites and/or involving mobile radar, as reported on interview. In the Combined Series larger percentages of case than

control matched pair fathers reported having been stationed at an air field (18.1% vs. 15.9%), at a radar park (5.6% vs. 3.6%), or at a missile site (1.8% vs. 0.4%), and/or having been in military units using mobile radar (6.9% vs. 5.5%). For each series the deviation was in the same direction, with two exceptions: in the Original Series, no fathers (neither case nor control) reported having been stationed at a missile site; and in the Current Series 7.6% case vs. 9.4% control matched pair fathers reported having been in units that used mobile radar. Current Series pooled fathers reflect the pattern of the matched pairs in each of the operations but show somewhat smaller differences.

Table R-15 presents a summary of interview responses to questions concerning paternal history of work in and/or near radar, microwave and/or x-ray, "in military service", and "outside the military" (Table R-15A); and "in and/or out of the military" (Table R-15B), prior to conception of the index case. Except for the tabulations involving exposure "outside the military" (and Original Series responses to with/near x-ray), there was a pattern of more case than control fathers reporting exposure. For Combined Series matched pairs, exposure prior to conception of index was reported as follows: near radar installation in the military, 7.4% case fathers vs. 4.8% control fathers; in and/or out of military near/around radar, 4.5% vs. 3.3%; while with/near x-ray showed a counterbalancing effect (3.9% vs. 3.8%) resulting from the Current Series and the Original Series deviating in opposite directions. The with/near "other radiation" also showed very similar values for cases and controls but did not involve opposing deviations (2.4% vs. 1.5%). Reported exposure outside the military was very low, especially for case fathers.

As the most likely source of paternal radar exposure (at least

for the time period of the Original Series) was in the military service and the original study's findings had suggested both an excess of radar exposure and of military service for case fathers in comparison with control fathers(3,5), a study objective was to investigate further not only the history of paternal radar-microwave exposure, but also military service, incorporating, insofar as possible, procedures for validating the data.

The documentation of the military service history (particularly prior to conception of the index child) is pertinent both to Specific Aim 1 (stated above and in Appendix A) in terms of comparing parents "with regard to any occupational or military sources of radioactive substances or radiation" as well as items I and VIII of the Summary of Workscope outlined in the Winter 1969-1970 proposal (See Appendix A).

"Original Series

I. To locate the fathers of cases and controls in the original January 1, 1946 to October 1, 1962 series and bring their records up to date, obtaining more detailed information on military service and radar exposure as well as their experience since our last contact... and

Both Series

VIII. To validate paternal military/radar history by independent search of government military files on all fathers irrespective of service/ radar report".

Thus, the observations with regard to Military Service presented in this section pertain not only to Specific Aim I herewith being reported but also to I and VIII of the itemized aims of the Workscope.

Military Service of Fathers: As discussed above under Method, detailed questions on military service were added to the Current Series interview, and a follow-up interview of the Original Series fathers carried out. In addition, as also indicated previously and referred to in the tables on Radar , there was the independent search of service records

on all fathers of both series carried out at the National Personnel Record Center-Military Records in St. Louis, Missouri (where the National Archives and Records Service, General Services Administration records are located). This search was done by staff personnel of the Follow Up Agency of National Academy of Sciences (NAS), experienced in this type of investigation. As previously indicated, neither NAS nor its staff personnel or any of those engaged in the search were given any information as to which names belonged to fathers of cases and which to controls. As a result of this search, an independent source of military service information and radar exposure was made available to supplement and compare with the interview response data.

It is also noteworthy that military service reporting on initial interview and/or follow-up interview was almost complete. While there were many fathers who had not served in the military, there were very few about whom information, in the affirmative or negative, was not obtained. Thus, in the Combined Series matched pairs, only 1.5% of case fathers and 0.6% of control fathers had an unknown military history.

The paternal military service data from interview and NAS search are presented in Tables MS-1 through MS-9. No attempt was made to obtain military service records or history on mothers.

Tables MS-1 through MS-4 are based on interview data only.

Table MS-1 gives the history of military service of fathers derived from their interview responses and tabulated to include total reported service irrespective of time relative to birth of index child. While in the Original Series a larger proportion of case than control fathers reported military service (63.5% vs. 57.0%), in the Current Series

matched pairs, although the overall frequency was slightly higher, the percentage of case fathers who reported having been in service was very similar to that of control fathers 72.7% vs. 71.1%. Thus, for Combined Series, matched pairs, the excess of case fathers observed (67.0% vs. 62.3%) was almost entirely due to the Original Series.

Table MS-2 gives the history of military service of Current Series matched pair fathers by branch of service and by time relative to conception of the index child, based on interview data only. Only for the Army was there a larger percentage of case than control fathers serving prior to the conception of the index child, 37.5% vs. 30.5%, and when including service during the year of conception, time unknown, 38.3% vs. 30.5%. No real excess of case over control fathers was reported in Navy, Marine Corps, Air Corps, Coast Guard, National Guard, or any service history.

A tabulation comparable to Table MS-2 is presented for Original Series matched pair fathers in Table MS-3. In that series, also, there was a higher percentage of case than control fathers reporting Army service prior [x] to the index conception (32.2% vs. 28.0%). Whereas a slight excess of case fathers reporting Marine Corps service prior to index conception also was reported, the numbers were small and do not vary more than the slight variation in absolute percentages noted for Navy or Coast Guard service.

Table MS-4 presents the interview-based history of military service by branch and time of service for the Combined Series matched

---

[x] NOTE: As noted above, in all tabulations of military service, radar exposure, etc., where time relative to the conception of the index child is indicated, priority is given to "time" before or "prior to" conception of the index. Therefore, if exposure extended over a period of time which overlapped, encompassed or included any time prior to index conception, even if the proportion of the prior exposure was very small relative to the total exposure, the exposure is, nevertheless, coded as "Prior".

pairs. As both the Original and Current Series had indicated that more case fathers than control fathers had served in the Army prior to conception of the index child, this pattern was clearly apparent in the total combined tabulation (34.2% vs. 29.0%).

Military service as reported from the NAS record search is presented in Tables MS-5 through MS-8, with an overall summary in Table MS-9, which gives a comparison of the interview and NAS-based information.

Table MS-5 (based on NAS data) summarizes record of military service of fathers reported by NAS in comparison with interview reporting, irrespective of time relative to conception of the index child and branch of service. Military service was verified by NAS for a slightly larger percentage of case than control fathers in the Combined Series matched pairs (62.5% vs. 56.1%), with the excess more marked in the Original Series (59.7% vs. 50.9%) than in the Current Series (67.2% vs. 64.8%). Current Series pooled fathers reflected the same pattern as the Current Series matched pairs , which constitute most of the pooled subjects. In the Combined Series matched pairs, there were slightly fewer fathers of cases than of controls with no record from NAS and no service reported on interview (32.9% vs. 37.8%), the difference deriving mainly from the Original Series (35.6% vs. 42.6%), rather than the Current Series where the frequencies were very similar (28.1% vs. 29.7%). As for the proportion for whom there was no record found by NAS but for whom service was reported on interview (4.7% vs. 6.1% in Combined Series), the trend was in the same direction, although no real difference was noted for either the

Current or Original Series and the numbers were small. As a result, the total with no record found by NAS was lower for case than control fathers (37.5% vs. 43.9% in the Combined Series, 40.2% vs. 49.1% in the Original and 32.8% vs. 35.2% in the Current Series).

Table MS-6 presents NAS reported paternal military service by branch of service and time relative to conception of index child for matched pairs of the Current Series. All of the service reported encompassed the period prior to the conception of the index child. It is of interest that the difference between case and control fathers in the Army is somewhat less from NAS than indicated on interview as shown in Table MS-2: 37.5% vs. 34.4% from NAS compared to 37.5% vs. 30.5% on interview; and moreover that NAS reports 4% more Army service for control fathers, and that NAS indicates 4.0% fewer control fathers in the Navy (19.5% case vs. 15.6% control fathers in the Navy according to NAS report as compared to 19.5% for both case and control fathers according to interview responses). Thus, there is a data shift from Navy to Army service yielding not only a smaller case-control paternal difference in Army service but producing a slight excess in Navy service for case fathers as compared to control fathers.[x]

Table MS-7 presents corresponding tabulations of NAS reported history of paternal military service by branch of service and time for the Original Series matched pairs. Only for the Army was there any service reported that did not extend into the period prior to the conception of the index child (0.5% for case fathers and 0.5% for control fathers after conception of index). For the service "prior" to conception of

---

[x] See Table MS-9 for the tabulated summary comparison of NAS and interview reporting.

the index child, there was an excess of case fathers as compared to control fathers, in particular for the Army (37.0% vs. 29.2%), but also for the Navy (16.2% vs. 14.4%) and Marines (3.7% vs. 0.9%, p = .052). While the same trend was noted on interview (Table MS-3), the differences were not the same. Based on percentage of total subjects (See Table MS-9), NAS showed higher rates and a larger difference for Army service than interview (31.5% vs. 27.8%) whereas Navy rates were somewhat lower than interview (17.1% vs. 16.7%); and the Marine Corps. approximately the same.

The tabulation for the Combined Series is given in Table MS-8. Based on the NAS record search report only,6% more fathers of cases than of controls served in the Army prior to conception of the index (37.2% vs 31.1%), almost 3% more case than control fathers in the Navy (17.4% vs. 14.8%) with a similar trend suggested in the Marines (3.5% vs. 2.9%), although the last is entirely due to differences in the Original Series.

Table MS-9 summarizes the history of military service for Current, Original, and Combined Series by branch of service and time relative to conception of index child, allowing comparison of data from the interview responses and from the NAS search of records. The findings are reviewed in summary below.

Summary of paternal military service experience for the Current, Original, and Combined Series from interview and NAS report: Although the interview data did not indicate any striking difference between cases and controls in total military service for either series, the almost 5% excess in case fathers of the Combined Series matched pairs, Table MS-1, 67.0% vs. 62.3% disregarding time of service relative to conception of

the index child, derived almost entirely from the Original Series (63.5% vs. 57.0%) rather than from the Current Series (72.7% vs. 71.1%). In the Current Series matched pairs, 93 of the 128 case fathers and 91 of 128 control fathers served in some branch of the service.

When military service was examined relative to the probable date of conception of the index child, almost all of the service was reported to have overlapped into a time period prior to conception, the time period of interest with regard to possible etiological or risk factors in Down's syndrome (Table MS-9). For paternal military service prior to conception of the index child, by branch of service for the matched pairs of the Current, Original and Combined Series, the data derived from (1) reporting of respondents at interview and (2) NAS reports tabulated separately revealed no striking patterns.

No sizable differences were observed between case and control fathers. The only suggestion of a deviation appeared in the higher percentage of case than control fathers in the Army prior to conception of the index child, and that was not statistically significant. In the Current Series, 38.3% vs. 30.5% for case and control fathers, respectively, on interview ($p = .19$), and 37.5% vs. 34.4% from NAS ($p = .61$) were noted. The trend in the Original Series was similar to the Current Series with regard to Army service, except that the larger deviation between case and control fathers appeared in the NAS report rather than in the interview data, (31.5% for case fathers vs. 27.8% for control fathers on interview, 37.0% vs. 29.2% from NAS). For Marine Corps service, the deviations in the Current Series and

Original Series were in opposite directions. The Current Series showed a slightly lower proportion of case than control fathers in the Marines (3.9% vs. 7.0% on interview; 3.1% vs. 6.3% on NAS report), whereas the Original Series showed more case than control fathers in the Marines (3.7% vs. 1.4% from interview; 3.7% vs. 0.9% from NAS report approaching significance only in the latter situation, p = .052) resulting in a counterbalancing in the Combined Series (3.8% vs. 3.5% on interview; 3.5% vs. 2.9% from NAS). None of the other services showed any case control differences in the Original or Current Series, and consequently only the deviation in the Army service remained in the Combined Series: 34.0% case fathers vs. 28.8% control fathers on interview (p = .14); 37.2% vs. 31.1% on NAS report (p = .09). With all branches of the service considered together, there was a slightly higher frequency of case fathers than control fathers with a history of military service in the Combined Series (from interview, 64.2% vs. 61.3%, p = .61; from NAS, 61.3% vs. 54.6%, p = .13). Most of the difference derived from the Original Series (on interview, 60.2% vs. 56.5%, p = .61; from NAS, 58.8% vs. 49.5%, p = .11), rather than the Current Series (on interview, 71.1% vs. 69.5%, p = .89; from NAS 65.6% vs. 63.3%, p = .78). Thus the larger percentage of case fathers with military service prior to conception of the Down's cases suggested in the Original Series was not as apparent in the Current Series; and the Combined Series did not show any marked difference between case and control fathers in military history.

This was of particular interest since in contrast to the suggestion noted previously in the Original Series [3], the Current Series did not yield evidence of any kind suggesting that case fathers had an excess of radar-microwave (or other radiation) exposure from any

sources inside or outside the military, as compared to controls.

Maternal Occupational Radar-Microwave and Other Radiation Exposure History

As for mothers' responses to questions concerning radar-microwave and/or other radiation exposure, there were very few affirmative replies. Consequently, no tabulations are presented here. Instead, the data are summarized below. No Current Series mothers (case, control, matched pairs or pooled groups) reported having worked with radar or microwaves of any type. Two case mothers (of 149 for whom information was known) reported having worked near radar installations, but no control mothers.

It should be noted that the radar questions had not been included in the interviews of mothers in the original study, and that the follow-up contact of fathers for radar-microwave and military service information did not include re-interview of mothers, except by happenstance when fathers were being traced. In terms of cost-benefit considerations, the logistics and likely productivity clearly did not warrant further exploration along those lines, in view of the paucity of maternal occupational and/or military exposures indicated in the Current Series interview, which did include more detailed questioning on such exposures.

Consequently, there was also no attempt to document maternal military service or to carry out an independent search of maternal service records.

Nevertheless, maternal occupational exposures or potential exposures to radiation sources were examined insofar as possible from the interview responses to occupational history as well as the direct

radar-microwave-radiation questions. Also, in addition to the general classification of maternal occupations into the standard categories used for socioeconomic indexes (shown in Table SO-1), responses were scrutinized in regard to possible exposure risk occupations.

As for direct responses in the Current Series indicating occupational x-ray exposure prior to conception of the index child, there was no difference between case and control mothers in the matched pairs or in the pooled groups. From matched pairs, 5 of 125 case mothers about whom information was known and 5 of 126 control mothers with known information, and from mothers of pooled cases, 6 of 147, as compared to 5 of 147 mothers of pooled controls, reported occupational x-ray exposure. With regard to work near "other radiation", 2 case mothers (of 128 in matched pairs and of 149 in pooled groups) among the mothers with known history reported such exposure, but there was no known exposure among corresponding mothers of controls.

With regard to responses to radar and radiation questions, there was insufficient evidence of any definite exposure prior to conception of the index child to make any inferences. Among the matched pairs, 2 case mothers (1.6%) and no control mothers reported having worked with or near radiation. Occupational history was unknown for 2 of the control mothers. Among additional/"unmatched" mothers, one control mother had an unknown history of exposure and no case mothers reported exposure.

From the general maternal occupational history obtained in the Original Series initial interview, some maternal occupational exposure was suggested: 7.9% of case mothers and 3.3% of control mothers had worked in a professional or technical capacity, with 8 case and 3 control

mothers giving actual history of x-ray and/or fluoroscopic exposures.

Perusal of interview responses of mothers of the Current Series regarding their occupational history yielded the following: Among the mothers of Current Series Down's cases providing informative responses, there were 13 nurses and nurses' aides (10 and 3 respectively) as compared to 7 nurses and 3 medical and/or laboratory technicians among mothers of Current Series controls. Six case mothers worked at Bendix and/or Westinghouse as compared to 5 control mothers; one case mother reported military service. In all, 20 case mothers and 15 control mothers from the Current Series had occupations in paramedical, military, or industrial fields that might have involved radiation exposure.

Taken together, it is estimated that in the Combined Series, 37 case mothers (20 from Current and 17 from Original Series) and 22 control mothers (15 from Current and 7 from Original Series) had worked in medical or technical occupations and/or indicated x-ray and/or fluoroscopic exposures. The pattern is suggestive and interesting, but no attempt at further validation on a retrospective basis was considered feasible for mothers, as this exposure was not traceable primarily to any one industry, place of employment or source, but rather to a wide range of private employers, including physicians and some short-term employment sources. It was clearly unlike the situation with fathers, where military exposure was by far the major source, making a systematic search of government records a feasible, although enormous undertaking.

SPECIFIC AIM 2.

To compare parents of Down's syndrome cases with parents of matched controls with regard to medical radiation exposure (diagnostic

and/or therapeutic): e.g., individual x-ray photographs, fluoroscopic radiation; ingestion or injection of radioactive substances, such as ^{131}I, ^{32}P, etc; implantation of radon seeds; cobalt radiation; and any other diagnostic or therapeutic procedures involving ionizing radiation.

Parental Medical Radiation. Among the findings of particular interest in the Original Series was parental exposure to radiation prior to the conception of the index child. The exposure of Current Series mothers and fathers, respectively, to medical radiation is summarized in Table MED-1A for the period prior to conception of the index child; and in Table MED-1B for the period including first month of pregnancy as well as definitely prior to conception. In contrast to the Original Series, which showed a significant difference in the percentage of case and control mothers who reported having no medical radiation prior to the index child's birth (50% vs. 59.9%), there appeared to be no difference in the Current Series between the percentage of case and control mothers of matched pairs reporting "no radiation" of any type prior to conception of index child (64.5% case mothers vs. 62.8% control mothers, $p = .79$). That the percentage reporting diagnostic radiation is exactly the same for Current Series cases and controls (19%) is not inconsistent with the lack of a case-control difference in diagnostic radiation in the Original Series. In regard to other types of radiation, whereas in the Original Series case mothers had significantly increased exposure both to fluoroscopy and to therapeutic radiation prior to the birth of the index child, the pattern was not consistent in the Current Series and did not reach statistical significance for either. More Current Series case than control mothers indicated "therapeutic radiation only (7.4% versus

3.3%); and, summing over the pooled categories (i.e., therapeutic alone or with either or both diagnostic and/or fluoroscopic), the apparent difference decreases only slightly (9.1% versus 5.8%, p = .67, still NSD). On the other hand, in summed categories for fluoroscopy, more control mothers than case mothers of matched pairs (13.2% versus 8.3%, p = .21, NSD) appear to have had such exposure prior to conception of index child. Including exposure during the first month of pregnancy, as shown in Table MED-1B, the patterns are similar to those for "prior to pregnancy" except for much more overall exposure to both case and control mothers, thus a decrease in those reporting none and an increase in those with diagnostic procedures only and in combination. The excess of case mothers reporting therapeutic radiation remained: for "therapeutic only" category (5.6% for case vs. 0.8% for control mothers of the matched pairs), though in total combinations involving therapeutic radiation, the difference did not increase.

Thus, while the Original Series showed significantly increased medical radiation of mothers of Down's cases prior to the index birth, with most of the exposure difference mainly from fluoroscopic and therapeutic radiation and combinations thereof, the findings in the Current Series are much less clear. Not only is there no difference between case and control mothers of the Current Series reporting medical radiation prior to conception and through the first month of pregnancy, but there also appears to be a contrasting pattern in therapeutic and fluoroscopic radiation, i.e., Current Series case mothers have slightly, but not significantly (p = .67), more therapeutic radiation than control mothers, while Current Series control mothers have more fluoroscopic radiation than case mothers (NSD). Nor does it appear that the difference in tabulation base between the Original and Current

Series could account for the discrepancy in the findings for the two series: i.e., the Original Series computations are based on exposure prior to the birth of the index child, the Current Series computations deal with exposure prior to conception and/or during the first month of pregnancy.

Tables MED-2A and MED-2B summarize maternal and paternal diagnostic x-ray exposures by site of exposure for Current Series. Table MED-2A gives the distribution by site for x-rays known to have occurred prior to conception of index child; Table MED-2B gives the distribution by site not only for those x-rays known to have been definitely prior, but also includes those taken during the year of conception (i.e., thus including those which may have occurred prior to conception but for which exact dating is uncertain).

Table MED-2A shows a larger percentage of control than case mothers (pooled and matched pairs) with x-rays at each site (except chest-pooled), gallbladder, kidney, including IVP, stomach-intestinal-abdominal, and other organs. A similar pattern appears when fathers of matched cases and controls were examined, except for chest x-rays. Among pooled case and control fathers, there is a slight deviation in the opposite direction for most sites, but none of the differences approach statistical significance.

Table MED-2B, which includes the extra, less specific time period (i.e., exposure during the year of conception as well as prior to con-

ception), shows a pattern similar to the tabulation for prior only, both for mothers of matched pairs of cases and controls and for pooled mothers. Otherwise, the tabulation for fathers (matched pairs and pooled) for the extended time period yields trends similar to those observed in the tabulation limited to exposures prior to conception only, including the directional differences (particularly for pooled fathers with case fathers exceeding control fathers in frequency of chest and gall bladder radiation). As none of these "differences" attain statistical significance, the findings may be spurious and no causal inferences can be made.

Table MED-3A concerns maternal fluoroscopic exposure prior to conception of the index child and Table MED-3B, the "prior" period plus unspecified times during the pregnancy year. There is no evidence of any greater exposure among mothers of cases as compared to mothers of controls; and, in fact, more case mothers than control mothers report no chest, abdominal, or other fluoroscopic exposures. The pattern is almost identical, whether tabulation is limited to exposures definitely prior to conception (Table MED-3A) or whether it also includes the year of pregnancy, when specific date is unknown (Table MED-3B).

Table MED-4 summarizes maternal therapeutic radiation for Current Series matched pairs by site of exposure (and/or condition involved) and time of exposure (prior to conception of index child and after the birth of the index child respectively). Reported exposure is extremely low both for the entire period prior to conception and afterward. The only

site/condition involving more than 2 mothers is the skin-warts-birthmark grouping, for which 6 case mothers and 5 control mothers received therapeutic radiation, certainly no discernible difference.

Table MED-5A i and ii gives number of fluoroscopic sessions prior to conception for case and control mothers (matched pairs and pooled) by maternal age at conception of index child. It is of interest that a lower frequency of case than control mothers in the matched pairs (8.2% vs. 15.0%) reported any fluoroscopy. When unmatched[x] cases and controls were included, the number of case and control mothers was almost identical: 20 case mothers as compared to 21 control mothers (14.1% vs. 14.9%).

Table MED-5B provides the same type of tabulation prior to birth rather than prior to conception of the index child. Still the pattern is the same, a lower frequency for case than control mothers of matched pairs (8.2% vs. 17.1%) and also for pooled (7.7% vs. 16.7%).

Radioactive Substances Ingested or Injected.

From the interview responses to questions on injected radioactive materials, neither the Current Series nor Original Series yielded any report of an injection of radioactive substances prior to conception of the index child among the mothers of cases. On the other hand, one mother of a Current Series matched control reported having an injection of a radioactive material prior to conception of index child; and another Current Series matched control mother reported having an injection during the year of pregnancy. No unknowns were recorded on interview among Current Series case mothers, whereas among Current Series control mothers, one matched control and one additional control mother were recorded as unknown. In the Original Series one matched pair case mother

[x] "Unmatched" parents refer to mothers and fathers of "additional" and "questionable" Down's cases and "additional" controls who are not in any of the matched pairs. "Pooled" includes "unmatched" as well as members of matched pairs.

had an injection of a radioactive substance at an unknown time, seven case mothers (six from matched pairs and one mother of a questionable Down's case) were recorded as "unknown" for radioactive injections, and two control mothers were listed as unknown.

As for the ingestion of radioactive materials, 1 of 128 Current Series case mothers and 2 of 128 Current Series control mothers from among the matched pairs reported drinking radioactive materials at some time prior to conception of the index child. In the Original Series, 1 of 216 case mothers but none of the matched control mothers reported ingesting radioactive materials prior to the birth of the index. However, after the index birth, four case mothers and four control mothers reported having drunk radioactive materials, and one control mother did so at an unknown time. Six Original Series case mothers (5 from matched pairs and one mother of a questionable Down's case) and 3 control mothers were listed as unknown with regard to ingestion of such substances.

Fathers: With regard to radioactive materials injected, one control father and no case fathers in the Current Series matched pairs reported such an injection prior to the birth of the index, while 1 matched pair case father and 1 "additional" control father reported an injection after the index birth and 1 matched control father, during the year of the index birth. In the Original Series 1 case father had an injection at an unknown time and no control fathers reported injections, with 7 case fathers and 2 control fathers of that series recorded as unknown.

Ingestion of radioactive materials prior to the birth of the index subject was reported for 1 case father and 2 control fathers from the Current Series matched pairs, and 1 case father but no control fathers

from the Original Series matched pairs: thus for the Combined Series 2 case fathers vs. 2 control fathers. Two control fathers from the Current Series matched pairs and 4 each of case and control fathers from Original Series matched pairs had drunk radioactive materials at some time after the index birth. In the Combined Series, 11 fathers were recorded as unknown: 2 from Current Series controls, 6 from Original Series cases and 3 from Original Series controls.

It is thus apparent that there are no discernible differences between parents of cases and parents of controls either from the Current Series or the Original Series as to injection or ingestion of radioactive substances; and that total reported exposure for all categories is extremely low. Whether these observations result from gross underreporting (intentional, or due to lack of knowledge of medical use of these substances, or recall failure) or whether there is actually a very low level of exposure, remains to be determined.

SPECIFIC AIM 3

To compare the parents of Down's cases and of controls with regard to other factors (socioeconomic status, religion, menstrual and medical history, marital history, etc.) recognized or suspected to be associated with the occurrence of Down's syndrome and to examine the possible interaction of such factors with radar and ionizing radiation exposure.

In an attempt to delineate clues as to maternal and/or paternal factors of etiological significance in Down's, a number of sociobiological characteristics were examined in the Current as well as the Original Series.

No differences were observed between the parents of cases and the parents of controls in such socioeconomic indicators as occupation, education, or any other characteristics examined.

Socioeconomic Status (SES). The education and occupations of Current Series parents have been used as indicators of socioeconomic status (SES).

Education of parents. A comparison of the educational background of mothers of cases and controls in the Current Series (Table S-1) showed no striking differences. A pattern of more clustering was suggested in the middle groups for case mothers (82.6% vs. 76.6% from "elementary and some high school" through "some college"), while a slightly larger proportion was noted at the extremes for controls ("elementary school or less" and "college graduates"). The educational status of fathers of cases and controls also was similar; however, a smaller proportion of case than control fathers had some college education, graduate and/or professional training, apparent in both matched pairs and pooled fathers (29% vs. 35% for matched pairs only and 26.8% vs. 35% for pooled fathers excluding those with unknown educational background).

Occupations of parents. There did not appear to be any significant difference in the occupations of Current Series fathers of Down's cases and controls, whether only matched pairs were considered or all pooled cases versus pooled controls (Table SO-1). There was a suggestion of fewer medically oriented "professionals" among fathers of cases than of controls, but the difference was negligible (13.5% vs. 12.7%) when that category was combined with "other professionals" (clergymen, artists, etc.).

There also seemed to be relatively more craftsmen among case than control fathers (34.1% vs. 25.4%) and fewer operatives (15.1% vs. 19.8%). However, all of these slight deviations are within the reasonable expectancy of normal variation.

As for mothers' occupations, most Current Series mothers reported "none", with a tendency toward a slightly larger percentage among mothers of cases: 62.5% vs. 55.2% for matched pairs; 62.0% vs. 56.2% for pooled. There appeared to be somewhat fewer operatives (blue collar and industrial workers) and possibly service workers among mothers of cases than of controls (Table SO-1).

Occupations considered with regard to possible exposure to radiation (radar-microwave, ionizing radiation, radioactive substances, etc.) have been discussed above. The number of subjects involved, however, is so small that no tabulations are presented with regard to types of occupations involving exposures. Responses to questions concerning paternal work with microwave, radar and other radiation in the military as well in civilian occupations are tabulated above (See R Series Tables, including Tables R10-15).

Religion of parents. Another social parameter of interest is religion. In the Current Series, tabulation of religious preference showed the patterns for parents of cases and controls to be not significantly different, although some minor variation was observed. Among mothers (Table S-2), none of the control mothers and only 1.3%-1.6% of the mothers of cases reported "no religion". A slightly larger proportion of case than control mothers were Roman Catholic (53.1% of matched pair and 51.3% of pooled case mothers as compared to 46.9% and 47.0% respectively

of control mothers), and a slightly smaller proportion of case than control mothers were Jewish (1.6% and 1.3% for matched and pooled case mothers respectively vs. 3.9% and 3.4% of control mothers), in contrast to the Original Series, where there was a higher frequency of Jewish as well as Catholic parents. The trends were similar for fathers (Table S-2), except that the slight variation between case and control mothers was even less apparent for fathers, although the directional patterns were the same for case versus control parents in reporting no religion, Roman Catholic, and Jewish affiliations. Thus, the suggested larger proportion of Catholic and Jewish mothers and fathers of cases than of controls observed in the Original Series was not confirmed in the Current Series. While the Current Series did have more Catholic mothers of cases than of controls, the difference was not significant and hardly discernible in fathers; the trend was in the opposite direction for Jewish parents of cases and controls.

Reproductive (Pregnancy, Obstetrical and Menstrual) and Marital Experience of Mothers of Cases and Controls. The reproductive patterns and marital history of mothers were examined in some detail for the Current Series - the former, investigated because of the contradictory reports in the literature (46-77), despite the lack of significance in the Original Series; the latter, because of marked differences noted between case and control mothers in the Original Series.

Current Series maternal marital history before marriage to the father of index child is given in Table MR-1 for matched pairs of cases and controls, while Table MR-2 summarizes total maternal marital history irrespective of whether before or after the index birth. Pregnancy

history and fetal wastage prior to and subsequent to the index birth are presented in Tables MR-3 (Matched Pairs) and MR-4 (Pooled Groups). Menstrual history is given in Table MR-5.

The marital history of mothers of cases and controls is of interest since the Original Series showed that a significantly higher percentage of case mothers had been married more than once. Table MR-1 summarizes for the Current Series the marital history prior to the father of the index for mothers of cases and of controls, tabulated by maternal radiation exposure prior to conception and/or during the first month of pregnancy. Radiation was unknown for 3 case and 3 control mothers among the 128 matched pairs. Of the total 128 case and 128 control mothers, 20 case mothers (15.6%) and 17 control mothers (13.3%) had been married more than once prior to their marriage to the father of the index child (not significantly different). In view of the association of Down's with maternal medical radiation exposure observed in the Original Series, it appeared desirable to examine the maternal marital history, controlling on radiation in that Series. Consequently, this was also done in the Current Series for comparison purposes. Among those mothers reporting any type of medical radiation, a larger percentage of mothers of controls (14.5%) than of cases (11%) had been married prior to marriage to the father of the index child. Moreover, it is of interest that (1) this difference derived primarily from mothers who had diagnostic x-ray rather than fluoroscopic or therapeutic procedures, which involve higher dosages and (2) that the only hint of an excess of multiple marriages among case mothers did not appear in those with radiation exposure, but rather in those reporting a negative radiation history

(20.9% case vs. 11.9% control mothers with multiple marriages prior to index child, p = .26, NSD). Thus, in the Current Series there was not a significant excess of multiple marriages prior to the birth of the index child among mothers of Down's cases; and, whatever deviations did appear were not positively correlated with maternal radiation exposure prior to conception of the Down's case. Finally, considering total marital history and disregarding relationship to time of index birth, (Table MR-2), 19 control mothers as compared to 20 case mothers had multiple marriages, i.e., clearly no difference in marital history of case and control mothers, prior to the index child or at any period.

As for pregnancy history and wastage, in the Current Series matched pairs (Table MR-3) and pooled groups (Table MR-4), there was a suggestion of some deviations not found in the Original Series. Mothers of Down's cases had fewer pregnancies prior to the birth of the index child than mothers of matched controls (364 vs. 418 pregnancies, p = .055). There also appeared to be a slightly higher rate of fetal loss prior to the birth of the index child, (16.2% vs. 14.8%, p = .67, NSD). The difference in fetal loss seemed even more marked after the birth of the index child, when case mothers appeared to have slightly more pregnancies than control mothers (58 vs. 51 in matched pairs); the fetal loss rates in case mothers being almost double that in control mothers, although not reaching statistical significance (32.8% vs. 17.6%, $p = > .10$). In the Original Series the total pregnancies of mothers of Down's cases deviated slightly in the opposite direction from the pattern shown in the Current Series both prior and subsequent to the index child, without any excess of fetal loss subsequent to the index birth. The possibility that the seemingly high rate of fetal wastage following the birth of the Down's

case in the Current Series might be an artifact must be considered, i.e., resulting from induced abortions which were less likely to have occurred and/or be reported in the earlier period. It, therefore, seemed possible that the excess of fetal loss in case mothers following the index child is not of etiological significance, especially in view of the absence of any such difference prior to the index birth. Combining the findings on matched pairs of the Original and Current Series tended to counterbalance any minor case-control deviations that were suggested when the two series were examined separately. No real differences remained between case and control mothers other than a slightly smaller number of pregnancies prior to the index child among case mothers. The pattern in pooled case and control mothers (Table MR-4) was similar to that observed in the matched pairs.

The menstrual history of mothers from the matched pairs of the Current Series is given in Table MR-5. As in the Original Series, the mothers of cases and controls were strikingly similar in age at menarche, duration of and intervals between periods, as well as regularity of menstrual periods. While mothers of Down's children reported a very similar mean age at menopause, of those in menopause, slightly fewer case than control mothers indicated operative menopause. As well over 85% of mothers were still menstruating at the time of interview, it is certainly not realistic to speculate as to the possibility of differences with such a markedly truncated distribution.

In all, case and control mothers were not remarkably different in their menstrual and reproductive history. Although some of the deviations attained borderline significance, many may be spurious or artifactual (e.g., increased abortions subsequent to Down's cases). Where patterns

in the Original and Current Series do not show similar deviations (number of pregnancies prior to index pregnancy; maternal age distribution during prior pregnancies, marital history), caution is needed in interpretation to avoid overspeculation.

Medical History: In addition to maternal menstrual and reproductive (fertility, obstetrical, etc.) factors suggested by a number of investigators as possible correlates of Down's, most prominent among factors in medical history considered as possible putative agents have been maternal thyroid disorders (77-89, 71, 75). Interview information, indicating possible thyroid dysfunction and aberrancies, was examined and is summarized in Table T-1, which is limited to thyroid history prior to conception of the index child, and Table T-2, which includes the year of conception as well as the period definitely prior to conception. The mothers of Down's cases and controls were strikingly similar in regard to all evidence of thyroid problems. No mothers of either cases or controls from matched pairs of the Current Series reported having thyroid surgery prior to conception of the index. While the same number of Current Series case and control mothers from matched pairs reported having taken thyroid medication (10 of 128), only 2 of 128 case mothers and 5 of 128 control mothers reported thyroid "treatment". Only one of the 128 case mothers and 2 of the matched control mothers reported having thyroid tests. The same pattern appeared in Table T-2.

While the Original Series had not revealed any differences between case and control mothers in medical history, the published literature has suggested an association of not only thyroid aberrancy but also other maternal medical conditions with Down's syndrome. (See Table 1). Therefore, the interview responses of mothers were

examined not only as to evidence of thyroid conditions (thyroid disease, thyroid medication, diagnostic and therapeutic thyroid x-irradiation, and ^{131}I ingestion) but also positive replies concerning diseases of the adrenals, liver, or kidneys; hypertension; rheumatic heart disease; diabetes; tuberculosis; leukemia; anemia; cancer of any type; non-malignant tumors; convulsive disorders, epilepsy; hearing or visual defects; and infectious and/or childhood diseases, such as chicken pox, mumps, poliomyelitis, etc. (Tables MH-1 through MH-15). There was a low rate of positive responses for all but childhood diseases. No discernible differences between case and control mothers appeared, except for nephritis (7.8%, 10/128 case mothers vs. 3.9%, 5/128 control mothers) and for anemia and other blood disorders (20.3%, 26/128 vs. 13.3%, 17/128). While these few differences could have occurred by chance, especially considering a large number of conditions, they are, nevertheless, worthy of further investigation in other series.

SPECIFIC AIM 4

To examine the chromosomes of the fathers with a history of exposure to radar and unexposed fathers of children matched to them, and to compare findings.(x)

Chromosome Studies.(x) Chromosome studies were carried out on radar exposed fathers and the unexposed fathers matched to them. "Matching", as for the study of parental factors in the Original and Current Series, refers to matching the index child by hospital of birth, sex, race, maternal age, and date of birth. Note, however, that the matched pairs for comparison here were not necessarily fathers of Down's versus fathers of controls, but rather radar-microwave exposed fathers versus unexposed fathers of matched children, irrespective of whether

(x) As noted above, effects observed in paternal peripheral blood are being used as an indirect indicator of likelihood of microwave associated effects on chromosomes of the germ cells as well as somatic cells.

the child was case, control, or "new match". The different sources of matched pairs are listed in <u>Figure 1</u> and <u>Table CS-1</u>, with the numbers of subjects in each combination given in the latter. Fifty-five matched pairs composed of definitely radar exposed and unexposed fathers, 7 pairs of fathers who had worked near radar and their unexposed controls, and 38 unmatched exposed, near exposed, and unexposed, fathers comprise a total of 162 fathers for chromosome study (<u>Table CS-1</u>).

The chromosome findings were classified into 4 groups - A, B, C, and D:

<u>A</u> group includes long #2 chromosomes, long short arm on G chromosome, secondary constriction #1 or uncoiled #1, secondary constriction #9, fragile #16, prominent satellite on D, etc., i.e., cytological abnormalities likely of heritable type.

<u>B</u> group includes quadriradials, endoreduplication, fragmented chromosome(s), dicentric(s), double chromatid breaks, isochromatid breaks, strands between chromosomes, and other abnormalities which may be due to mutagens or unknown cause.

<u>C</u> group includes gaps, single chromatid breaks, and various abnormalities which may be due to technical error and/or have occurred in the previous 72 hours.

<u>D</u> group indicates "normality", i.e., no detected abnormalities, deviations, or aberrancies of karyotype such as those of A, B, or C type.

Illustrations of some of the types of chromosome aberrancy observed in the fathers studied are shown in the composite photomicrographs of Figure 2 and in Figure 3, endoreduplication.

<u>Table CS-2</u> summarizes the chromosome findings not only on exposed fathers and fathers "near" exposure as compared to the unexposed fathers matched to them, but also on unmatched exposed and

unexposed fathers studied. The distributions of mutually exclusive individual and combination categories are given in Table CS-2A: "B" meaning only "B" type deviations; AB, BC, ABC indicating B with A, with C, and with both, respectively, etc. Table CS-2B presents various summary overlapping (not mutually exclusive) categories. For example, "any B" includes B only, AB, BC, and ABC, thus B occurring alone or in combination with any other deviation. Although there are no striking differences between exposed and unexposed fathers, there are some findings of interest and some consistent, though not all statistically significant, trends. In the 55 pairs of exposed and unexposed fathers, fewer of the exposed fathers were found to be without any detectable chromosome deviations: 22/55 (40.0%) exposed vs. 25/54 (46.3%) unexposed fathers, p = .64. Including unmatched fathers, the frequencies were 39.1% (27/69) of the exposed vs. 48.4% (31/64) unexposed; differences still appear but are still not significant (p = .63). For those "near" exposure, 42.9% (3/7) were classified in the D group (normal) versus 71.4% (5/7) of their unexposed matches so classified (p = .60). Thus, 40.9% (36/88) of fathers with definite or possible exposure vs. 50.7% (36/71) of unexposed fathers had negative chromosomal findings (p = .28).

The most noteworthy difference was observed in type "C" abnormalities. For aberrancies in the "C only" category (although not statistically significant), there was almost a two-fold difference between the exposed fathers and their unexposed matches: 20% (11/55) as compared to 11.1% (6/54) (p = .31). With "near exposure" matched pairs included, the frequencies of the exposed were greater than twice the unexposed: 22.6% (14/62) versus 9.8%, (6/61), (p = .09). Limiting comparisons to definitely exposed matched and unmatched fathers

only (excluding "near radar" groups), the difference was only slightly reduced (18.8% vs. 12.5%, p = .55), and with all exposed matched and unmatched groups, including all degrees of exposure, the difference (20.5% vs. 11.3%) is similar to that for the matched pairs of exposed versus unexposed fathers (p = .20).

When all C type aberrancies are considered, irrespective of whether A or B types occur also, significantly more of exposed matched pair fathers (including both definitely "exposed" and "near exposure" in the exposed class) than their unexposed matches showed chromosomal defects: 40.3% (25/62) of the exposed fathers versus 21.3% (13/61) of the unexposed fathers matched to them, p = .04, or compared to all unexposed fathers, 21.1% (15/71) of whom had C aberrancies, p = .03. The differences, though still marked in absolute values, did not reach statistical significance when "near exposure" categories were omitted. Considering only matched pairs, 38.2% (21/55) of exposed fathers versus only 24.1% (13/54) of unexposed fathers showed the "defect" (p = .16); including unmatched fathers, still over 1/3 of the exposed (34.8%, 24/69) vs. less than 1/4 of the unexposed fathers (23.4%, 15/64), p = .21, or compared to all unexposed, 21.1% (15/71), p = .11, had the aberrancy detected.

Moreover, when considering A and/or C combinations, pooled exposed and"near exposure"fathers from matched pairs had a significantly higher rate of defects than pooled unexposed (43.5% vs. 22.5%, p = <.03); including unmatched fathers as well as all types of exposure, 39.8% exposed vs. 22.5% unexposed fathers showed these defects (p = <.03). Clearly, significant differences noted here derived largely from differences in

the frequency of C type aberrancies in exposed as compared to unexposed fathers, even though the differences in the "C only" category did not reach the .05 level of significance. These observations thus raise the question whether chromosome fragility or other effects of radar exposure are involved, or whether the observed C type deviations are, in fact, due entirely to technical error or artifacts.

As for B abnormalities, clearly the matched pairs did not show any differences in "B only" or "any B". On the other hand, when various combinations of any two abnormalities (AB, AC, or BC) were examined, the exposed fathers showed a higher frequency than the corresponding unexposed, except for BC in exposed unmatched fathers. Furthermore, the combination of all 3 types of aberrancies (ABC) appeared to be more frequent in exposed than unexposed fathers, although the numbers were extremely small.

When pooling all types of deviations (A and/or B and/or C), exposed fathers did appear to show higher frequencies not only in the matched pairs (60.0% of exposed fathers versus 53.7%), but also when unmatched fathers are examined separately (64.3% vs. 40.0%) or pooled with the matched (42/69, 60.9%, vs. 33/64, 51.6%). Moreover, even when the near exposure matched groups are considered separately (57.1% vs. 28.6%), or when all exposure groups - matched and unmatched, definite and near - are pooled (52/88 = 59.1%) and compared to all unexposed subcategories (35/71 = 49.3%), more exposed fathers than unexposed fathers showed one or more deviations.

Tabulations of detailed findings on chromosome studies are given in <u>Tables CS-3 - CS-8</u>. Among the 162 fathers whose chromosomes were

studied, 3 had cultures that failed to grow. All these failures occurred among unexposed fathers: one unexposed matched to an exposed father; two others, unmatched unexposed fathers.

Chromosomal variants classified in the A Category are given in Table CS-3: Long #2's, Fragile #16, Long Short Arm G, Secondary Constriction of #1 or Uncoiled #1, Secondary Constriction #9, and Prominent D Satellite. Considered by individual type of chromosome variation, the numbers of deviants are very small.

Long #2 chromosomes: Two fathers had long #2 chromosomes. It is of interest that both fathers with this variant were exposed fathers from the matched pairs.

Fragile #16: Two fathers showed fragile #16 chromosomes, one exposed unmatched father and one unexposed father matched to an exposed father.

Long short arm G: The only father with a long short arm G was an exposed father from one of the matched pairs. This aberrancy appeared to occur in all cells insofar as could be determined.

Secondary Constriction #1/Uncoiled #1: Two fathers, both exposed members from matched pairs, had a secondary constriction on chromosome #1 or an uncoiled #1. This appeared to occur in all cultured cells in one of these fathers but was observed in only one of the two successful cultures obtained on the other father.

Secondary constriction on #9: Only 1 father (an exposed from a matched pair) had a secondary constriction on #9. This was found in more than one cell but not discernible in all cells examined.

Prominent D satellite: Two fathers had prominent D satellites and these were detectable in all successful cultures. While one father

was an exposed member of one of the matched pairs, the other was an unexposed member of a matched pair.

The distributions of Type B abnormalities are given in Tables CS-4 and CS-5. Except for fragmented chromosomes and endoreduplication, the numbers in individual categories are small.

Strands between chromosomes: One exposed father from a matched pair had strands between chromosomes. This abnormality, classified as a B type, was presumed to be present in all successful cultures, although not always visible.

Quadriradials: Two fathers had quadriradials: One father, an exposed member of one of the matched pairs, had the quadriradial in only one cell of any culture; the other father, an unexposed father from a matched pair, had the quadriradial in successful cultures in one cell only, also.

Dicentrics: Five fathers had dicentrics. Two exposed fathers from matched pairs and one exposed unmatched father had the dicentrics in only 1 cell of any 1 culture. Two fathers (unexposed members of matched pairs) had dicentrics in one cell only in all successful cultures done.

Fragmented chromosomes: Twenty-seven fathers had fragmented chromosomes. Three exposed fathers (2 from matched pairs and 1 unmatched) had the fragmented chromosomes in more than 1 cell, but not all cells, in all successful cultures. Twenty-two fathers (3 exposed fathers from matched pairs, 5 unmatched exposed fathers, and 2 unmatched near exposed as well as 11 unexposed matched fathers and 1 unexposed unmatched, respectively) had them in only one cell of their cultures, but in all successful cultures done. Two fathers (one an exposed unmatched father and one an unexposed father from a matched pair) had fragmented chromosomes found in only 1 cell of any culture.

Double chromatid breaks: The distribution of 17 fathers with double chromatid breaks is also shown in Table CS-4. Three fathers had double chromatid breaks in more than 1 cell: 2 exposed fathers and 1 unexposed father from matched pairs. Thirteen fathers had this abnormality in 1 cell only per culture but in all successful cultures: 5 exposed fathers and 1 near exposed father from matched pairs, and 3 near exposed unmatched, as well as 4 unexposed matched pair fathers. One exposed matched pair father had this defect in only 1 cell of 1 culture.

Isochromatid breaks: One matched pair father who had been near exposure showed an isochromatid break in one cell of his successful culture(s).

Endoreduplication: Table CS-5 gives the distribution of 22 fathers whose chromosomes showed endoreduplication. Two matched pair fathers (one exposed and one unexposed) showed endoreduplication in more than one cell, although not in all cells, in all successful cultures. Nineteen fathers showed endoreduplication in 1 cell only, but in all successful cultures: 6 exposed and 10 unexposed fathers from matched pairs, as well as 1 unmatched exposed, 1 unmatched near exposed, and 1 unmatched unexposed father. One exposed matched pair father from a matched pair had endoreduplication in only 1 cell but not in all cultures.

Chromosome findings showing C type deviants, gaps and single chromatid breaks, are tabulated in Table CS-6.

Gaps: Table CS-6 gives the distribution of 35 fathers with chromosomal gaps. There were 6 fathers with more than 1 cell showing gaps in all successful cultures: 2 exposed matched and 1 near exposed matched as well as 3 unexposed matched fathers. Among the 27 fathers with gaps in all successful cultures but in 1 cell only, 14 were exposed fathers

from matched pairs and 3 near exposure from matched pairs, 1 an unmatched exposed father and 2 unmatched fathers near exposure as well as 6 unexposed fathers from the matched pairs and 1 unexposed unmatched father. Two other fathers showed gaps in at least one cell: one exposed matched father and one unexposed matched father.

Single chromatid breaks: Table CS-6 also gives the distribution of 23 fathers with single chromatid breaks. Three fathers, 2 exposed and 1 unexposed from the matched pairs, had single chromatid breaks in more than 1 cell. Of the 19 who had them in all successful cultures but in 1 cell only, there were 7 exposed, 1 near exposed, and 5 unexposed fathers from matched pairs, as well as 2 exposed, 2 near exposed, and 2 unexposed fathers who were unmatched. In addition, 1 unexposed father from a matched pair had 1 cell only with a single chromatid break.

In addition to these detailed distributions of types of deviants tabulated on the basis of individual fathers, distributions were also examined on the basis of number of deviant cells for fathers with different types of exposure and matching status.

Table CS-7 gives the distribution of number of abnormal cells per father by exposure and matching status of father. It is of interest that, of 6 fathers with abnormalities in all cells, 5 were exposed, and 1, an unexposed father from a matched pair.

Table CS-8 gives the distribution of chromosome findings (A, B, C and D types, and combinations thereof) by specimen sequence, paternal exposure - matching status, and category of deviant. Table CS-8A presents findings on fathers in matched pairs involving 129 successful cultures: 97 first specimens, 23 second specimens, 5 third specimens, 3 fourth specimens, and 1 fifth specimen. Table CS-8B presents findings on 38 successful cultures from unmatched fathers: 29 first, 6 second, and 3 third specimens.

In overview, with regard to the chromosome studies of exposed and unexposed fathers, there appear to be more detectable deviations from "normality" in the chromosomes of fathers with a history of radar and/or microwave exposure than in fathers with no known exposure, and this difference between exposed and unexposed fathers derives primarily from "C type" defects. With the large number of comparisons examined and the small sample size, the observed differences might very possibly be spurious. On the other hand, despite the small numbers in subcategories and difficulty in interpretation of types of deviations in terms of abnormality, these findings are of interest and deserve further study. As the blood samples were coded to avoid any identification in the laboratory of exposure status, these differences cannot be attributed to conscious or unconscious observer bias.

The above (pages 37-83) presents the findings derived from extending the scope of the investigation of "Parental Radiation and Down's Syndrome (Mongolism)", and examination of the data pertinent to the 4 SPECIFIC AIMS cited. These are summarized and their implications considered in the Discussion section below.

ITEMIZED TASKS UNDER SCOPE OF WORK

With regard to the specific items included in the project plan as indicated in the Contractor's Proposal,(x) each has been carried out and completed. Delineated by item proposed, they are as follows:

"ORIGINAL SERIES

> I. To locate the fathers of cases and controls in the original January 1, 1946 to October 1, 1962 series and bring their records up to date, obtaining more detailed information on military service and radar exposure as well as their experience since our last contact."

(x) See Appendix A for copy of Contractor's Proposals. Items here discussed are found on pp. 11-12, of b. Contractor's Proposal for Extension of Current Study, Winter 1969-70 extension.

An attempt was made to contact the families of all 216 matched pairs of cases and controls (432 families) to obtain follow-up interview on military service, radar exposure, etc. This effort was completed after extensive tracing, and as indicated in Table MS-1, information was obtained on all except 5 of the 216 fathers of cases and all except 2 of the 216 fathers of matched controls of the Original Series.

> "II. To obtain from the radar exposed fathers of cases and controls and the unexposed fathers matched to the radar exposed subjects blood samples for chromosome studies and to carry out complete chromosome analysis on these fathers in the Original Series."

After radar exposure status was determined by interview and/or record search, "exposed" fathers were contacted, blood specimens obtained, and chromosome analysis carried out. As indicated in Table CS-1, 32 exposed Original Series fathers (29 who became members of matched pairs and 3 who remained unmatched with an unexposed father) and 12 Original Series fathers reported to have been "near radar exposure" were in the final chromosome study group, in addition to 21 unexposed matches identified from the Original Series and 35 new matches obtained for that series, providing 56 more fathers in those various categories: a total of 100 fathers from the Original Series per se or involving new matches to that series.

"CURRENT SERIES

> III. To identify and trace parents of children with Down's syndrome born in the Baltimore area from October 1, 1962 to January 1, 1969 as well as from January 1, 1945 to December 31, 1945 and:
>
> A. Verify diagnoses."

As discussed above (in the section on Method), the procedure for identification and tracing of parents was similar to that followed in the Original Series [2-5], the initiation point being the identification of the index child (see above p.22 and ff) followed by verification of diagnosis. The procedure for index case documentation, including search of hospital records, birth certificates, etc., is discussed above

(pp. 25-28) and in Appendix C-1. For the Current Series, 150 Down's cases were thus finally identified, of whom 128 meeting all the criteria became members of matched pairs, 22 others were unmatched but included in the pooled series: 13 carried as additional cases although unmatched and 9 not meeting all the requisites for inclusion also carried in the pooled series only and unmatched. Table B-3 gives distribution of the study group of index children.

"B. Search birth certificates on these affected children."

Birth certificates were searched on all of the 150 Down's cases (including unmatched) that comprised the study group of the Current Series plus others who were rejected because they did not meet criteria, they could not be traced, their parents were unavailable for participation in the study, or there were other reasons for exclusion.

"C. Select controls matched to cases on hospital of birth, date of birth, maternal age, race and sex of infant."

Control children were matched by the procedure designated, and their hospital (delivery, birth and other) records and birth certificates searched (See pp. 26-27 and references #2-5). For the Current Series 150 controls were included for final analysis and of these, 128 were matched to 128 Down's cases, i.e., 128 controls in the "matched pairs" group.

"IV. To carry out interviews of parents of Down's cases of Current Series."

Instead of the originally estimated 95 cases and 95 controls, the Current Series was extended to include families of 150 Down's cases of which 128 were in matched pairs of cases and controls. Tracing, interviewing of mothers and fathers, and data collection

were completed on this number. It should be noted that, to complete this sample, tracing of a much larger number was required. After eliminating those rejected because of failure of cases to meet the pre-established criteria and/or parental unavailability, interview data were obtained on the mothers and fathers of 150 cases. Of those, 128 had matched controls on whom parental interviews were also obtained, thus completing the 128 matched pairs.

> "V. To trace the matched controls of the Current Series and interview their parents."

Of over 150 controls whose parents were traced and interviewed, 128 were matched to documented Down's cases meeting the study criteria. These 128 constituted the controls referred to when the "matched pairs" are considered. Interview data for both mothers and fathers of those matched controls were obtained.

> "VI. To validate selected portions of the data obtained by interview against medical records in Current Series."

Validation of data on the index cases and their matched controls through birth certificate, hospital and other medical records available was carried out; and, in addition, validation of interview data on parental radiation and other interview questions, as feasible, was also undertaken. These attempts at verification of collected information were made in addition to the extensive validation of military service and military occupational history performed on both the Current and Original Series by search of government records arranged through NAS. (See also VIII below.)

"VII. To obtain blood samples and carry out chromosome analysis on all fathers reporting radar exposure and on the corresponding fathers of children matched to those whose parents were exposed in the Current Series."

Blood collection and chromosome cultures were completed on 162 fathers, including 62 matched pairs of exposed and unexposed fathers, and 38 unmatched fathers, derived from the Original Series and new matches, as well as the Current Series. Because of culture failures on 3 fathers, chromosome analysis was completed on 159 of the 162 fathers. (See Tables CS-1 through 8). Of the matched pairs, 16 pairs were exposed fathers of Down's cases and their matched control fathers who were unexposed (8 Original Series pairs and 8 Current Series pairs); 3 pairs were fathers of Down's cases classified as "near exposed" and unexposed fathers from their matched controls (2 Original Series pairs and 1 Current Series pair). Matched pairs of exposed control fathers and the unexposed fathers of cases to whom they had been matched comprised 13 pairs involving definite exposure (4 from the Original and 9 from the Current Series), and 1 pair from the Current Series involving near exposure. In addition, there were 23 exposed fathers: 9 Down's (6 from Original and 3 from the Current Series) and 14 Controls (11 from the Original and 3 from the Current) in pairs with new matches, as well as 3 near exposed fathers (1 Down's and 2 Controls) from the Original Series paired with new matches. Three pairs consisted of exposed and unexposed new matches. Among unmatched fathers there were 3 Original and 2 Current Series exposed Down's, 4 Current Series exposed control fathers, 2 near exposed Original Series Down's fathers, 5 near exposed fathers of Original Series controls, 1 unexposed Current Series Down's and 7 unexposed Original Series control fathers. Blood was collected on all of these fathers, after interviews concerning microwave exposure

status were completed. As noted above, this group of 100 Original Series and 62 Current Series fathers on whom blood was collected involves fathers not only of cases and of controls but also 23 new matches. The new matches comprise those matched to exposed fathers (to 6 Original Series and 3 Current Series exposed Down's and to 11 Original Series and 3 Current Series exposed Control fathers), 3 pairs of new match exposed fathers and new match unexposed fathers selected initially for the Original Series, and 2 new matches to Original Series Near Exposed Control fathers and on one for an Original Series near exposed case father. Among unmatched fathers there were 5 Exposed New Matches (3 Original, 2 Current), 5 Near Exposed New Matches (4 Original and 1 Current) and 4 Unexposed New Matches (2 Original and 2 Current Series) on whom bloods were collected for chromosome studies.

In summary, chromosome analyses were completed on 159 of the 162 fathers distributed as indicated above in Table CS-1. Where blood cultures failed to grow, an attempt was made to obtain additional specimens, until a satisfactory culture was available or further attempts were no longer feasible, and/or father was no longer available (x). While initially, additional specimens were to be sought when an abnormality was detected, that plan became too expensive and was discontinued, since in terms of cost-benefit analysis, it was more practicable

---

(x) Table CS-8 gives the distribution of chromosome results by specimen and paternal matching and exposure status.

to concentrate available effort , time and funds on obtaining at least one satisfactory culture per father selected for study. Thus in the final chromosome study group, at least one successful culture had been obtained on 159 fathers. (See Tables CS-2 through CS-8.)

"BOTH SERIES

> VIII. To validate paternal military/radar history by independent search of government military files on all fathers irrespective of service/radar report, (as well as carry out chromosome studies indicated above under II and VII respectively)."

As discussed in the section on Method of Study, an arrangement was made with the National Academy of Sciences Follow Up Agency to search military records on fathers of all Down's cases and fathers of their matched controls (as well as new matches). The records were searched (by the NAS staff) in the National Personnel Records Center - Military Records, in St. Louis, Missouri, a repository maintained by the National Archives and Record Service of the General Services Administration. Tabulations based on the findings are included in tables on military service and radar exposure (See MS and R Tables). Note in particular Table MS-5 Status of Record of Military Service Received From NAS.

(iv) DISCUSSION, CONCLUSIONS AND OVERVIEW

While some of the findings of the original Hopkins study of parental factors and Down's syndrome [1-5] were confirmed in the current study, this was not true of all. On the other hand, some new observations are quite provocative and require further investigation.

The maternal age effect in Down's syndrome clearly remains unchallenged; and the previously reported lack of an effect of advanced paternal age in Down's syndrome was confirmed in the Current Series. The menstrual and reproductive experience of mothers of cases and controls remains unremarkable, except for the suggestion in the Current Series (not found in the Original Series) of a possibly smaller number of pregnancies prior to the birth of the index child in mothers of Down's syndrome cases than among controls ($p = .055$). Examination of reported thyroid disease, medication, and/or other indicators of thyroid and other significant conditions in medical history (e.g., diabetes; tuberculosis; rheumatic heart disease, chicken pox, measles, mumps, poliomyelitis; hypertension; diseases of the adrenal glands or liver; leukemia, cancer of any type; non-malignant tumors; convulsions and/or epilepsy; and visual or hearing defects) also revealed no differences between mothers of Down's cases and of controls.

Clearly not confirmed in the Current Series was the excess of multiple marriages prior to the index birth observed in the Original Series suggesting, as conjectured at the time it was reported initially, that the finding in the Original Series was probably fortuitous.

Of particular interest is the absence of a difference in medical radiation history between case and control parents, shown not only in fathers of the Current Series (consistent with the observations on the fathers of the Original Series) but also in mothers of the Current Series (in contrast to the findings in mothers of the Original Series). Exactly the same percentage of Current Series case and control mothers (19%) reported on interview that they had had "no radiation" prior to conception of the index child. Nor were there any significant differences between case and control mothers in the various types of radiation, - the only suggestive deviation occurring in therapeutic radiation (still NSD). Unlike the Original Series, in which there was an excess of both therapeutic and fluoroscopic radiation in case mothers compared to control mothers, the Current Series did not show such a pattern in fluoroscopy. One may speculate as to whether there has been an increasing awareness in the medical community concerning the health hazards of ionizing radiation to women prior to child-bearing, resulting in much more restricted radiation exposure in the more recent period of the Current Series (1962-8) - except as required for therapeutic purposes - than

in the years preceding the birth of the Original Series children (1946-62). If so, it is not surprising that the only suggested case-control difference (still not statistically significant) occurred in the therapeutic radiation category and in combinations involving therapeutic radiation. As therapeutic radiation is less a matter of choice than necessity, reduction in usage is not as readily accomplished. Also to be taken into account is that the radiation history based on interview information is subject to problems of biased recall. Although hospital checking was carried out, x-rays taken in private physicians' offices were not screened. Moreover, not all Baltimore hospitals were screened for years prior to the index birth, and no out-of-city hospitals were included.

Also of particular interest is the lack of confirmation in the Current Series of a higher frequency of paternal radar-microwave exposure among fathers of Down's cases suggested in the Original Series. The replication study, using both interview data and an independent search of military records, not only found no excess of radar exposure in fathers of Current Series cases, but, in fact, showed a slightly higher frequency in control fathers which counter-balanced the Original Series differences, to yield almost identical frequencies in cases and controls in the Combined Series. This similarity in frequencies was also clearly apparent when consideration was limited to record search data from NAS only. As the military record search was carried out without the searchers' knowledge of which subjects were parents of Down's syndrome cases, the problem of possible biased reporting by respondents was controlled.

With regard to military service, more fathers of cases than of controls in the Current Series indicated Army service prior to birth of the index child, a pattern similar to that found in Original Series fathers. However, there was no excess of Marine Corps service for Current Series case fathers, as was observed in the Original Series case fathers. Consequently, in total military service (all branches combined, i.e., any branch), Original Series case fathers showed a greater excess over control fathers (60.2% vs. 56.5% from interview and 58.8% vs. 49.5% from NAS) than observed in the Current Series (71.1% vs. 69.5% from interview and 65.6% vs. 63.3% from NAS). Although, for the Combined Series pooled military service, (i.e., any branch), there was still a discernible difference remaining, more marked from NAS record search (61.3% vs. 54.6%) than from interview (64.2% for case fathers vs. 61.3% for control fathers), none of the differences were statistically significant.

The implication as to etiology of Down's syndrome of an excess of military service among fathers of cases in the absence of any discernible excess of radar-microwave exposure could pose a dilemma. On the one hand, the suggested (though NSD) variation in military service, is most heavily influenced by the Original Series deviation; on the other hand, unlike the radar, there appears to be slightly (although still not significantly) more military service in case fathers of the Current Series.

Examination of the chromosome findings suggests that a larger proportion of the cultures from radar exposed than from unexposed fathers had discernibly deviant chromosomes. The classification of detectable chromosomal deviations from so called normality is necessarily a very general one. It might be postulated that (1) damage from extrinsic agents (such as radiation and chemical mutagens) might be expected to result in the "B" type aberrancies, (2) that the "C" type might tend to be attributable, at least in some instances, to technical errors and/or to have occurred within the previous 72 hours, and (3) that the "A" type might involve heritable aberrations, transmitted through the germ line over generations. Since the categorization of chromosomal changes may be somewhat artificial, the distribution of observations was examined in several ways: by "A", "B", "C", "D" type deviations, by combinations of A-B-C types, and by individual aberrations within the "A", "B", "C" classes (e.g., secondary constriction #9; fragmented chromosome,gaps, etc.). Moreover, in view of the uncertain nature of what constitutes "near exposure," the chromosomal effects were examined not only for fathers classified as "exposed" as compared to "unexposed,"(and mainly for the matched pairs),but also for others of the various combinations of exposure status, pooled groups, etc. It is of interest that there appeared to be a consistent association of chromosomal aberrancy with exposure, even "near exposed"; and that the aberrancy was attributable primarily to "C" type defects. Differences between radar exposed (including those

AD-A061 593 JOHNS HOPKINS UNIV BALTIMORE MD SCHOOL OF HYGIENE A--ETC F/G 6/18
PARENTAL RADIATION AND DOWN'S SYNDROME, WITH PARTICULAR ATTENTI--ETC(U)
JUN 76 B H COHEN DADA17-69-C-0154

UNCLASSIFIED NL

2 OF 5
AD
A061 593


593

near-exposure as well as definitely exposed) and unexposed fathers attained statistical significance for "any C" defects and for "A and/or C" defects at the .02 and .03 level depending on specific comparisons. Whether the apparent excess of variants in radar exposed fathers was due to artifact, technical error, or was spurious, or, whether the observed variants did, in fact, indicate poorer ability to grow in culture, increased fragility of chromosomes or nuclear material, or some other direct or indirect effect of exposure, remains to be determined. Meanwhile, these chromosomal findings can only be regarded as suggestive, and warranting further, more refined types of studies. Clearly, they must be interpreted with caution, in view of the small numbers in subcategories and the difficulty in interpretation of types of deviations in terms of "abnormality".

In overview, it appears that neither the chromosome studies nor findings with regard to reported radar exposure differences yield definitive conclusions. Although the Current Series did not confirm the suggested excess of paternal radar-microwave exposure in fathers of Down's syndrome cases, the possible relationship of such exposure to increased risk of Down's offspring cannot be completely ruled out on the basis of these observations.

A number of problems were encountered in the study: some, of methodological nature, and others, in theoretical aspects of the approach.

One of the most challenging methodological problems of the investigation was the definition of radar "exposure". Since classification of fathers as "exposed" or "unexposed" proved to be quite complex, several sets of categories were used. Classification was based on interview report only, on National Academy of Sciences (NAS) search of military records with regard to exposure, and on combined information

from NAS and interview. The appropriate method for classification of chromosomal deviations from normality as well as the implications of the deviations also provided some difficulty in interpretation. Unavailability of fathers selected for study posed still another problem in the chromosome investigation: a number of fathers either were deceased, lived out of the area, refused to participate, could not be located, or were not available for other reasons. Finally, some of the blood samples obtained were unsatisfactory, failed to grow, and/or for technical reasons, an adequate chromosome analysis could not be made. Wherever possible, resampling was carried out, until a satisfactory chromosome analysis was obtained.

The conduct of a study that is sound in theory and rationale and at the same time logistically realistic and economically feasible was not practicable. Therefore, it was necessary to use an indirect approach to the problem. The examination of parental factors in Down's, utilizing a series of retrospectively ascertained Down's cases, is less than ideal. In view of the well established maternal age association and the recognized significant role of maternal factors in Down's, it would be expected that such factors would account for by far the major portion of the cases in a retrospectively ascertained series, masking any paternal factors. Moreover, the most severely affected radar exposed males (i.e., those with damage to germinal tissue) would be not only the ones with the highest risk of abnormal offspring, but also the most likely to have had somatic tissue damage with resultant poorer survivorship, eliminating them from the group ascertained through Down's offspring and alive for interview. Consequently, even if paternal exposure did actually increase the relative risk

significantly, this effect would be difficult to detect in a retrospective study of Down's cases and controls. Should a paternal relationship be discernible in such a study, it would suggest a very marked attributable risk and be a matter of considerable concern. That the Original Series did suggest a relationship may have been fortuitous. On the other hand, the observation requires definitive confirmation or rejection.

With regard to the Chromosome Studies, the observations, although also inconclusive, do suggest some effects of radar exposure and clearly warrant further investigation. Like the examination of paternal radar exposure in a series of retrospectively ascertained Down's cases, the study of chromosomes in the peripheral blood of radar exposed and unexposed fathers is not a sensitive approach to the study of radar effects on chromosomal aberrations in offspring, and is subject to the same pitfall: the likelihood of selective elimination from observation of the most severely affected. If radar exposure produces chromosomal damage, those with the most marked effects in the germ line would also have the most significant somatic effects and be the least likely to survive to ascertainment in a retrospective investigation. Even among those who did not have germinal damage but only somatic effects, those in whom the defective chromosomes persisted would have the highest mortality. Thus, those who are ascertained would be more likely to be those in whom the normal cells have selectively survived and the abnormal had been selectively eliminated, possibly making any original damage undetectable. Another unavoidable problem

would be the inability to detect abnormalities in the peripheral blood of individuals in whom only germinal damage without somatic damage had occurred. On the other hand, if chromosomal effects were observed in the peripheral blood of fathers after radar exposure, this would suggest long term and marked chromosomal damage, persisting from one to over 20 years after exposure. With such demonstrable somatic effects, the likelihood of accompanying genetic damage would warrant serious attention. Whereas not finding these effects in a retrospective study would not indicate that radar exposure has no deleterious effects on chromosomes in the germinal tissue or on the somatic tissue, observing persistent chromosomal manifestations clearly warrants further investigation.

In view of the suggestive findings of the Original Series with regard to a possible radar association, it was certainly necessary to investigate this question further. The *initial steps were taken*. A replication study was the simplest, least expensive, immediate approach. Supplementing it with the independent search of service records added an objective index, eliminating any possible differential in parental responses. The chromosome studies provided an additional type of information. Even if they did not offer a very sensitive means of obtaining evidence of microwave-induced chromosome effects, they did constitute another objective indicator that again was simpler and less expensive than a prospective study. These methods having been attempted with inconclusive findings, it is now necessary to look to the prospective, longitudinal, surveillance studies to resolve the issue.

TABLE 1

POSTULATED ETIOLOGICAL FACTORS AND CORRELATES IN DOWN'S SYNDROME □

Factor	References:
Age:	
Maternal Age: Positive correlation with incidence	7-31
Other maternal age relationships:	
Sex difference relative to maternal age	32-35
Incidence in younger mothers	36-40
(See also "Early Aging of Mothers" below)	
Paternal Age: Lack of association with advancing age	41-45, 18, 46
Parental Age and Delayed Fertilization	47-51
Grandparental Age and Parental Mosaicism	52, 13, 44, 53-56
Constitutional & Other Host Factors:	
Reproductive Factors: Gonadal, hormonal, obstetric, etc.	11, 57-58, 12, 59-66, 46, 48, 67-77
Endocrine Factors: Thyroid	78-86, 72, 87-90, 76
Adrenal and other	61, 64
Early Aging of Mothers	91-95
Marital History	48-50
Environmental Agents:	
Drugs and Other Chemicals	96-98
Viral and Other Microbial Agents	99, 13, 100-130
Seasonal Factors and Clusters	99, 60, 13, 44, 100, 131-132, 102, 107, 109, 22, 133, 36, 134, 76, 135-136
Radiation: Ionizing	60, 137-141, 69, 142-150
Non-ionizing △	151-155, 4, 156-165
Familial Cytogenetic Abnormalities:	
Familial Translocations	168, 79, 169-170, 27, 171-180
Parental Mosaicism (See "Grandparental Age & Mosaicism" above)	181-202, 56, 203
Related Chromosomal Aberrancies	204-213, 117, 214-232

□ Most of these aspects have been reviewed by Lilienfeld and Benesch, 1969, by Penrose and Smith, 1966, and by contributors to the Ann. N. Y. Acad. Sci., 171(2), 1970.

△ Primarily general chromosomal effects in man and experimental organisms, but not with specific reference to Down's syndrome.

FIGURE 1

STUDY DESIGN AND SOURCE OF STUDY SUBJECTS

PARENTAL FACTORS (e.g. Radiation exposure, etc.)

Down's Cases versus *Matched Controls*

Original Series	Born Jan. 1946 - Sept. 1962
Current Series	Born Oct. 1962 - Dec. 1968 1945

SOME UNMATCHED

Down's
Questionable Down's
Controls

CHROMOSOME STUDIES IN FATHERS

Radar Exposed Fathers (Original & Current Series) versus *Matched Unexposed Fathers* (Original & Current Series)

Matched Pairs

Exposed Down's Fathers	vs.	Unexposed Control Fathers
Exposed Control Fathers	vs.	Unexposed Down's Fathers
Exposed Down's Fathers	vs.	Unexposed New Matches
Exposed Control Fathers	vs.	Unexposed New Matches
Exposed New Matches	vs.	Unexposed New Matches

FATHERS OF NEW MATCHED

Matched Pairs
(Unexposed)
(Exposed)

Unmatched Fathers
(Unexposed)
(Exposed)

TABLE B-1a

STIGMATA IN CASES OF DOWN'S SYNDROME OF CURRENT SERIES
128 Matched Cases

Stigmata	Present		Absent		Questionable		Not Mentioned		Unknown	
	No.	%	No.	%	No.	%	No.	%	No.	%
Brachycephaly	61	47.65	9	7.03	1	0.78	57	44.53	0	0
Slanted palpebral fissures	94	73.43	3	2.34	0	0	31	24.21	0	0
Epicanthic folds	99	77.34	7	7.03	1	0.78	21	16.40	0	0
Palmar simian lines	86	67.18	18	14.06	1	0.78	22	17.18	1	0.78
Malformed ears	71	55.46	17	13.28	0	0	40	31.25	0	0
Broad and/or short neck	52	40.62	15	11.71	0	0	60	46.87	1	0.78
Web neck	19	14.84	27	21.09	3	2.34	79	61.71	0	0
Malformed fingers and/or hands	90	70.31	7	5.46	0	0	30	23.43	1	0.78
Nasal abnormality	71	55.46	11	8.59	0	0	46	35.93	0	0
Hypertelorism	30	23.43	20	15.62	1	0.78	77	60.15	0	0
Abnormal palate	57	44.53	7	5.46	0	0	63	49.21	1	0.78
Furrowed tongue	79	61.71	14	10.93	2	1.56	32	25.00	1	0.78
Abnormal footprints&/or handprints	45	35.15	0	0	0	0	80	62.50	3	2.34
Brushfield spots	50	39.06	26	20.31	3	2.34	49	38.28	0	0
Abnormal hip angles	15	11.71	17	13.28	3	2.34	87	67.96	6	4.68
Broad and/or short trunk	16	12.50	18	14.06	1	0.78	92	71.87	1	0.78
Congenital heart condition	59	46.09	52	40.62	4	3.12	13	10.15	0	0

TABLE B-1b

STIGMATA IN CASES OF DOWN'S SYNDROME OF CURRENT SERIES
150 Pooled Cases

	Present		Absent		Questionable		Not Mentioned		Unknown	
Stigmata	No.	%	No.	%	No.	%	No.	%	No.	%
Brachycephaly	71	47.33	11	7.33	1	0.66	67	44.66	0	0
Slanted palpebral fissures	110	73.33	4	2.66	0	0	36	24.00	0	0
Epicanthic folds	109	72.66	12	8.00	1	0.66	28	18.66	0	0
Palmar simian lines	99	66.00	19	12.66	2	1.33	29	19.33	1	0.66
Malformed ears	78	52.00	22	14.66	0	0	50	33.33	0	0
Broad and/or short neck	56	37.33	19	12.66	0	0	74	49.33	1	0.66
Web neck	21	14.00	33	22.00	3	2.00	93	62.00	0	0
Malformed fingers and/or hands	101	67.33	10	6.66	0	0	38	25.33	1	0.66
Nasal abnormality	80	53.33	13	8.66	0	0	57	38.00	0	0
Hypertelorism	34	22.66	25	16.66	1	0.66	90	60.00	0	0
Abnormal palate	67	44.66	9	6.00	0	0	73	48.66	1	0.66
Furrowed tongue	91	60.66	16	10.66	2	1.33	40	26.66	1	0.66
Abnormal footprints&/or handprints	50	33.33	3	2.00	0	0	94	62.66	3	2.00
Brushfield spots	56	37.33	31	20.66	3	2.00	60	40.00	0	0
Abnormal hip angles	17	11.33	21	14.00	4	2.66	101	67.33	7	4.66
Broad and/or short trunk	16	10.66	23	15.33	1	0.66	109	72.66	1	0.66
Congenital heart condition	68	45.33	58	38.66	6	4.00	18	12.00	0	0

Pooled includes additional and questionable Down's cases as well as matched pairs.

TABLE B-2 R

DISTRIBUTION OF DOWN'S CASES BY NUMBER OF STIGMATA

Current Series

Total Number of Stigmata	Stigmata Coded "Yes"				Stigmata Coded "Questionable"			
	Matched		Pooled		Matched		Pooled	
	No. of Subjects	%	No. of Subjects	%	No. of Subjects	%	No. of Subjects	%
0	0	0	2	1.33	106	82.81	124	82.66
1	0	0	2	1.33	21	16.40	24	16.00
2	1	0.78	2	1.33	0	0	1	0.66
3	5	3.90	6	4.00	1	0.78	1	0.66
4	5	3.90	6	4.00				
5	16	12.50	19	12.66				
6	15	11.71	17	11.33				
7	12	9.37	13	8.66				
8	14	10.93	17	11.33				
9	20	15.62	20	13.33				
10	8	6.25	11	7.33				
11	10	7.81	10	6.66				
12	12	9.37	14	9.33				
13	7	5.46	7	4.66				
14	3	2.34	3	2.00				
15	0	0	1	0.66				
Total	128		150		128		150	

Pooled includes additional and questionable mongols as well as matched pairs.

TABLE B-3

COMPOSITION OF STUDY GROUPS OF INDEX CHILDREN

	Down's Cases	Controls	New Matches
Current Series			
Conditionally accepted for study	165	162	
Eliminated because of:			
Incorrect diagnosis	5	0	
Refusal of parents	5	7	
Unable to locate parents	2	0	
Race & other reasons	3	0	
Control removed because case was removed	NA	5	
Total Eliminated	15	12	
Accepted for analysis (not all matched)	150	150	
Additional	13	22	
Questionable cases	9	NA	
Matched pairs	128	128	
Original Series			
Matched Pair Series	216	216	
Used for Chromosome Study but not in 216	6	5	
Total in Original Series & Chromosome Study	222	221	
New Matches in Chromosome Study			
Original Series			37
Current Series			11
			48

TABLE A-1

PARENTAL AGE DISTRIBUTION FOR DOWN'S SYNDROME CASES AND CONTROLS

Current Series Pairs Matched by Maternal Age

Parental Age	Mothers of:				Fathers of:			
	Down's		Controls		Down's		Controls	
	No.	%	No.	%	No.	%	No.	%
<20	6	4.7	6	4.7	2	1.6	1	0.8
20-24	18	14.1	17	13.3	15	11.7	13	10.2
25-29	18	14.1	20	15.6	19	14.8	20	15.6
30-34	25	19.5	25	19.5	27	21.1	24	18.8
35-39	38	29.7	36	28.1	26	20.3	23	18.0
40-44	22	17.2	24	18.8	27	21.1	31	24.2
45-49	1	0.8	0	0	10	7.8	12	9.4
50+	0	0	0	0	2	1.6	4	3.1
Total	128	100.1	128	100.0	128	100.0	128	100.1

The slight difference in the number of mothers of case and control children in each age group is due to the classification of the mothers into 5 year age groups.

TABLE A2

PARENTAL AGE DISTRIBUTION FOR DOWN'S SYNDROME CASES AND CONTROLS

Current Series Pooled

Age	Mothers of:				Fathers of:			
	Down's		Controls		Down's		Controls	
	#	%	#	%	#	%	#	%
<20	11	7.3	11	7.3	5	3.36	3	2.05
20-24	23	15.3	24	16.0	18	12.08	17	11.64
25-29	19	12.7	21	14.0	22	14.77	24	16.44
30-34	29	19.3	28	18.7	31	20.81	25	17.12
35-39	42	28.0	40	26.7	30	20.13	27	18.49
40-44	25	16.7	26	17.3	31	20.81	32	21.92
45-49	1	0.7	0	0	10	6.71	13	8.90
50+	0	0	0	0	2	1.34	5	3.43
Total	150	100	150	100	149	100	146	100

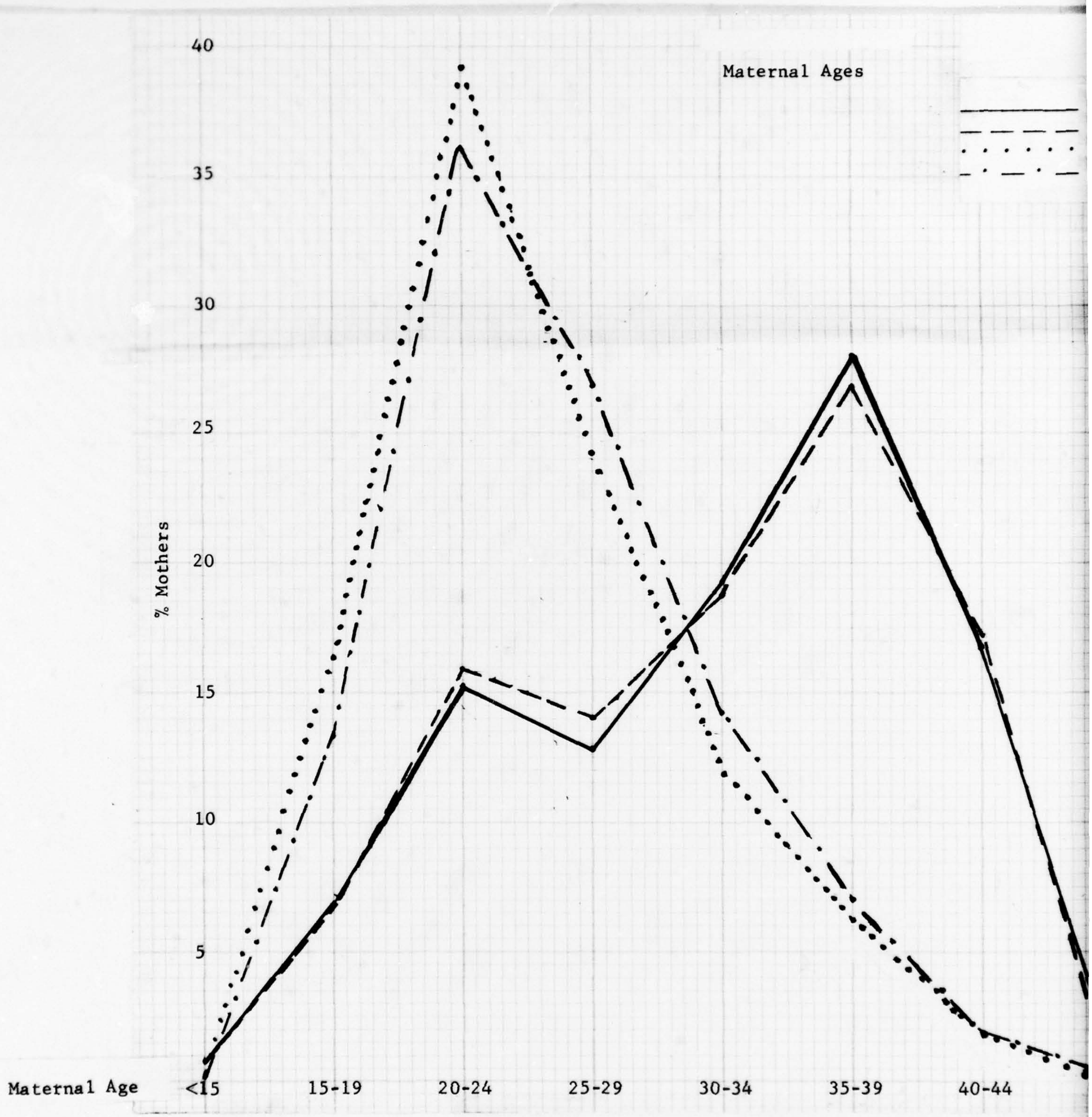
TABLE A-3

MATERNAL AGE DISTRIBUTION OF STUDY SERIES AND POPULATION COMPARISON SERIES FOR BALTIMORE AND MARYLAND

	Total White Births		Current Series				Original Series	
	Born 1963-1968		1962-1968 + Pooled ●		1962-1968 + Matched Pairs		1946-1962 Matched Pairs	
	Baltimore	Maryland	Down's	Controls	Down's	Controls	Down's	Controls
No.	56,190	342,963	150	150	128	128	216	216
Mat. age	%	%	%	%	%	%	%	%
<15	0.14	0.08	0.67	0.67	0.78	0.78	0	0
15-19	16.41	13.40	6.67	6.67	3.91	3.91	2.80	2.80
20-24	39.22	36.16	15.33	16.00	14.06	13.28	15.70	14.80
25-29	24.22	26.95	12.67	14.00	14.06	15.62	13.90	15.30
30-34	11.89	14.28	19.33	18.67	19.53	19.53	21.80	22.20
35-39	6.25	7.06	28.00	26.67	29.69	28.12	28.70	28.70
40-44	1.76	1.92	16.67	17.33	17.19	18.75	16.20	16.20
45 & over	0.08	0.10	0.67	0	0.78	0	0.90	0
Not stated	0.03	0.05	0	0	0	0	0	0

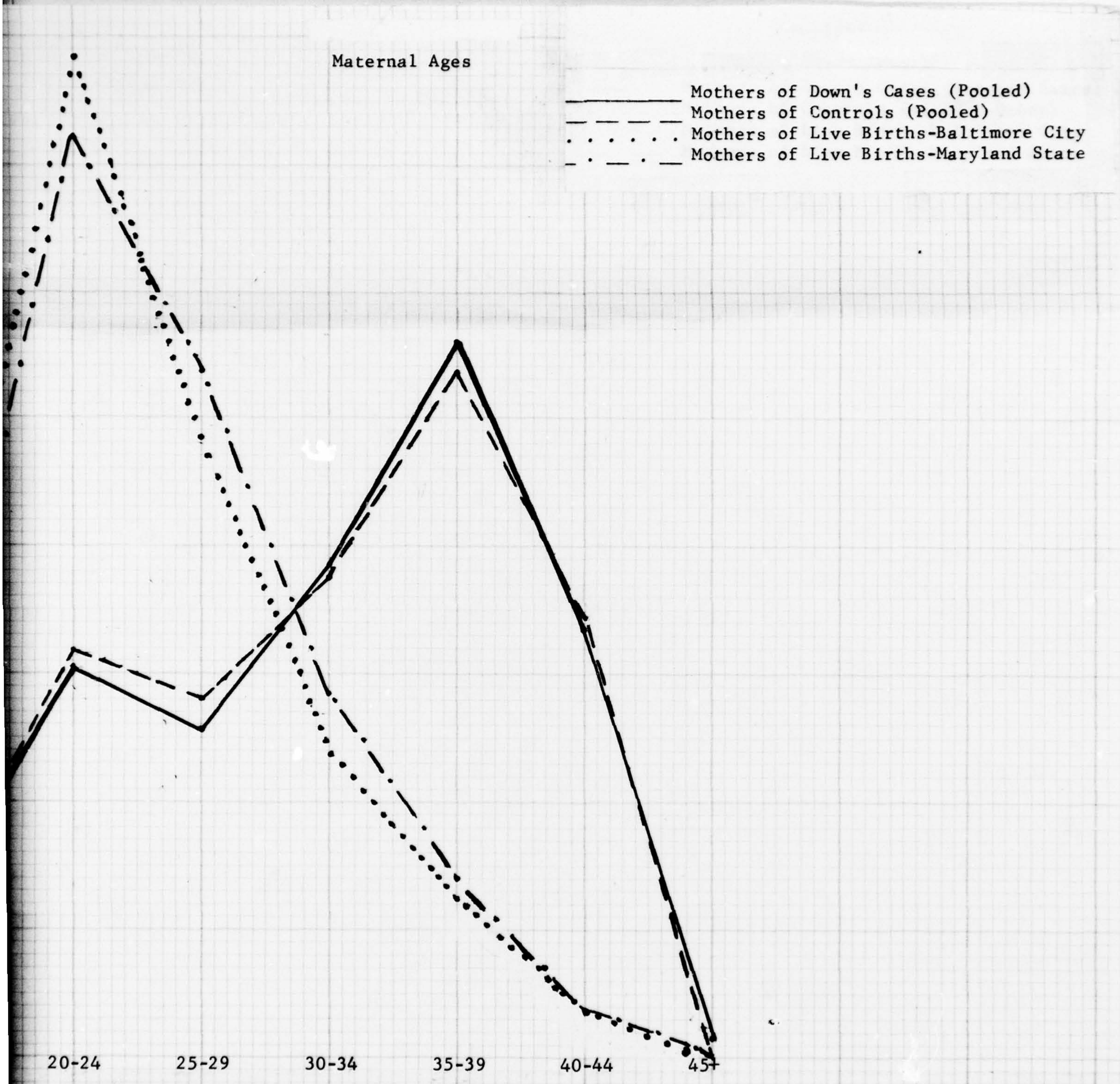
+ Including a few subjects born in the Original Series time period plus some 1945 births.

● Pooled includes mothers of additional and questionable cases and mothers of additional controls, as well as Matched Pairs.



Maternal Ages
% Mothers
40
35
30
25
20
15
10
5
Maternal Age
<15
15-19
20-24
25-29
30-34
35-39
40-44

108 Top half


Maternal Ages
Mothers of Down's Cases (Pooled)
Mothers of Controls (Pooled)
Mothers of Live Births-Baltimore City
Mothers of Live Births-Maryland State
20-24
25-29
30-34
35-39
40-44
45+

108 Top half

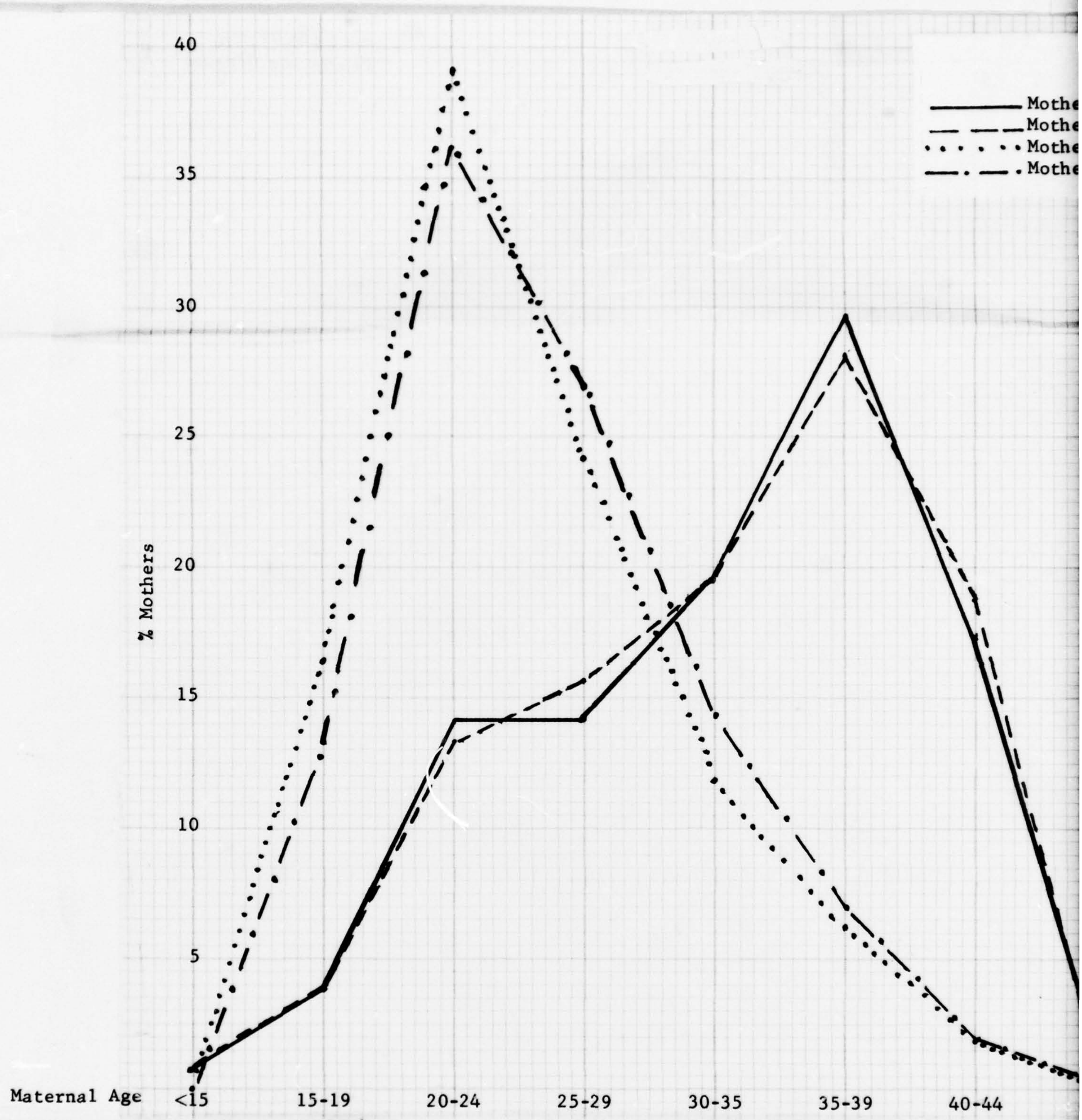
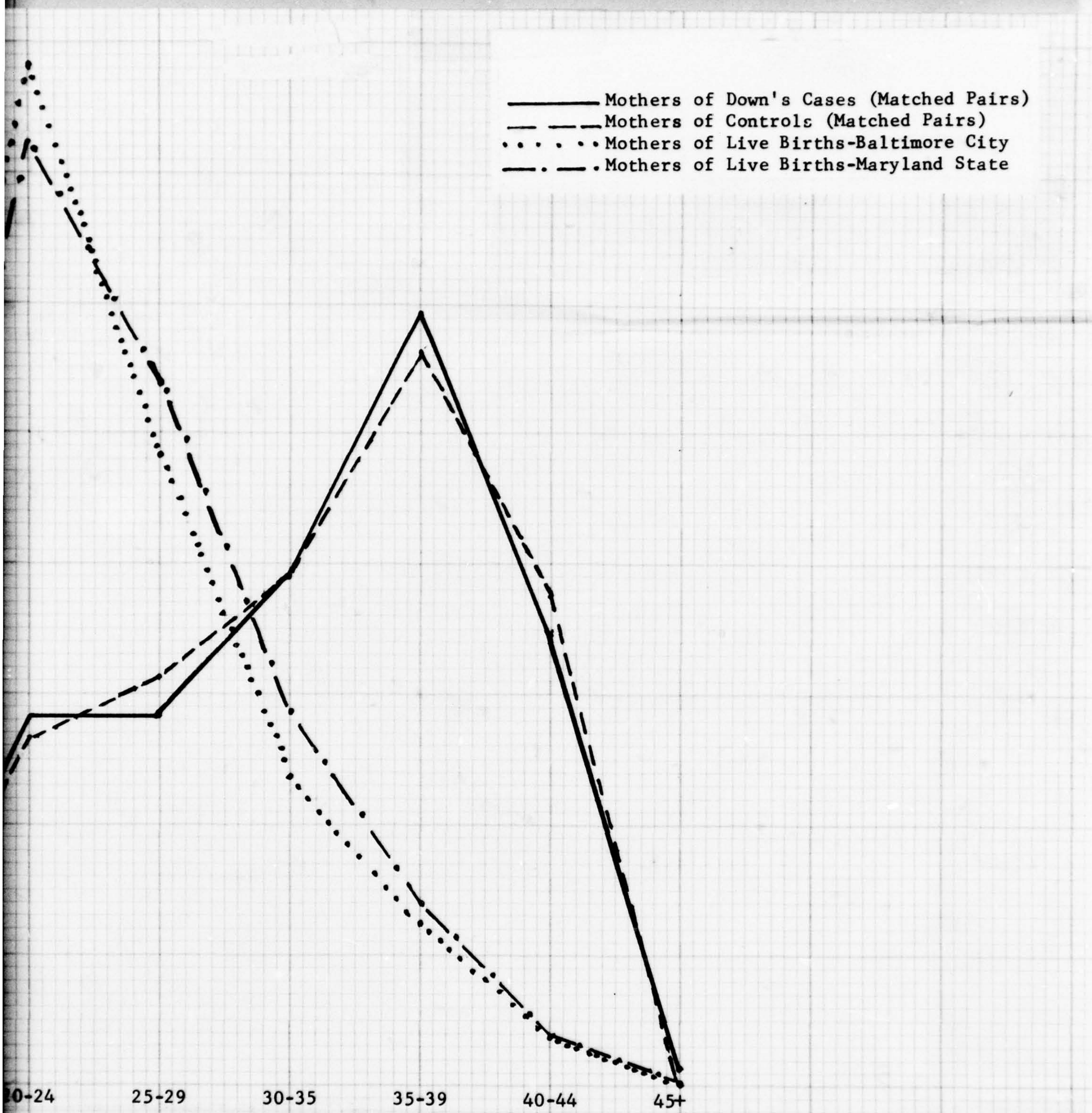


Fig. A-1 Maternal age distributions for Current Series Down's cases and controls (maternal age mat
Baltimore City and Maryland.

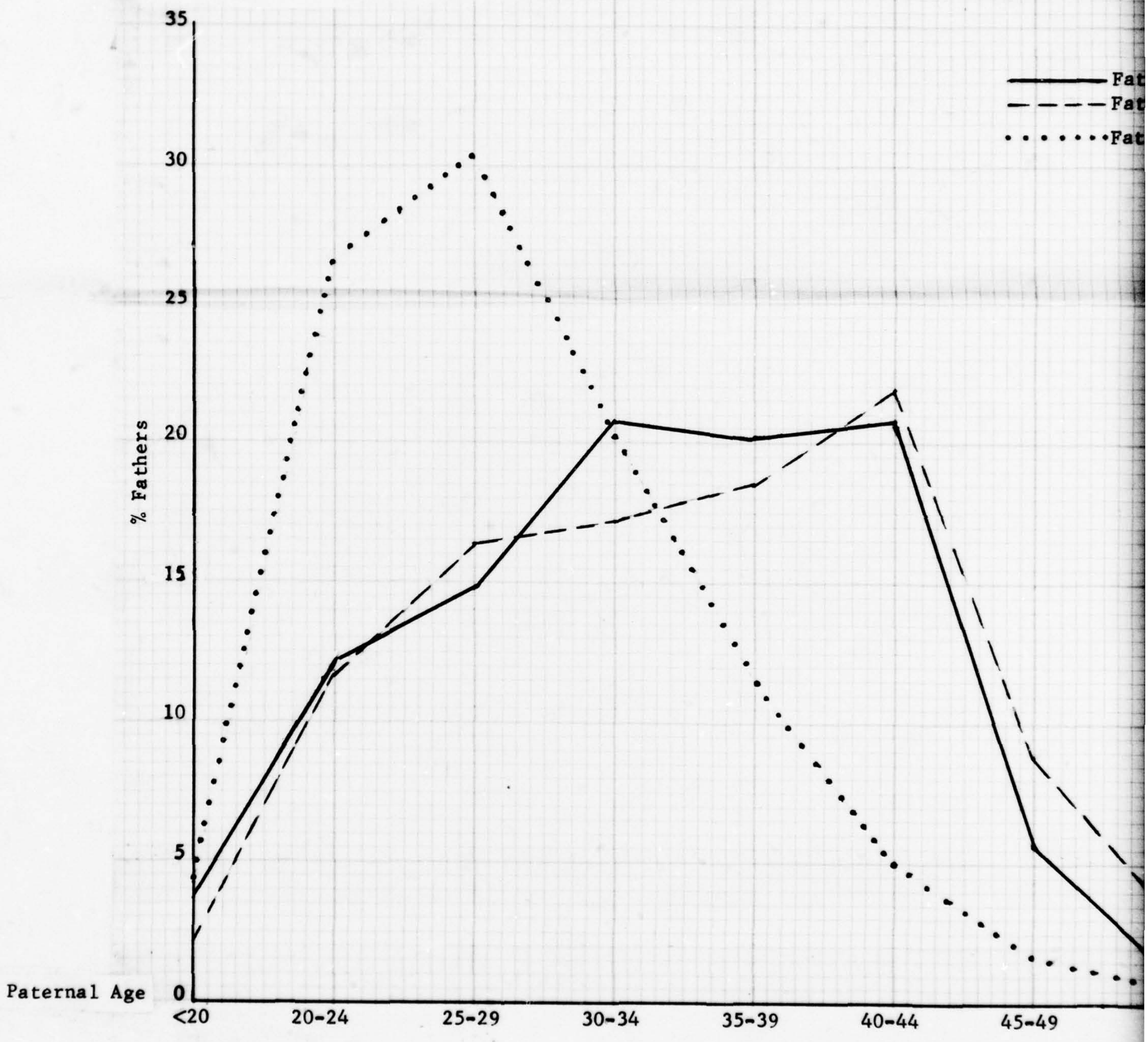
108 Bottom half



r Current Series Down's cases and controls (maternal age matched) and 1963-1968 white births for

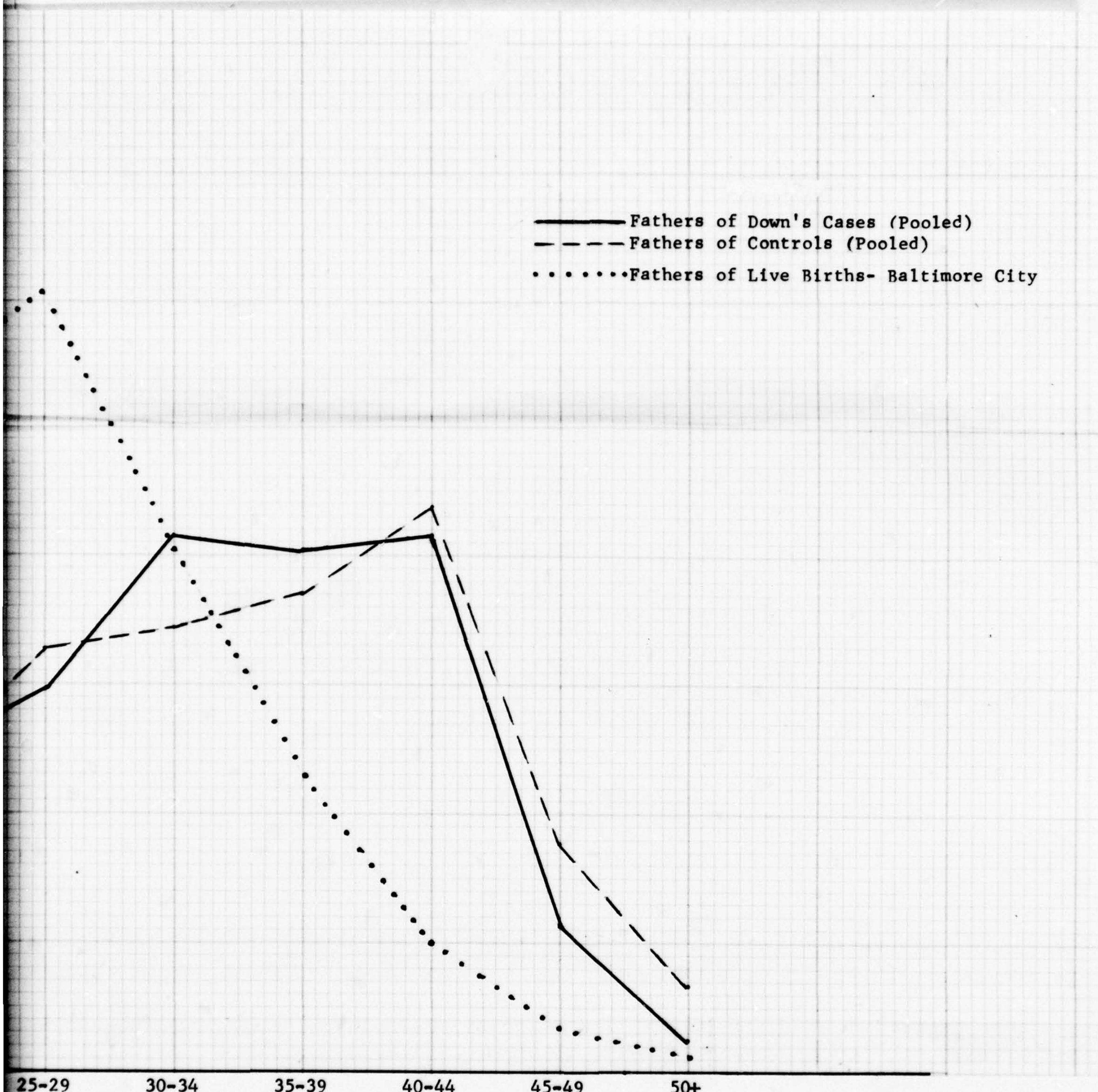
108 Bottom half

2



35
30
25
20
15
10
5
0
% Fathers
Paternal Age
<20
20-24
25-29
30-34
35-39
40-44
45-49
Fat
Fat
Fat

109 Top half



109 Top half

2

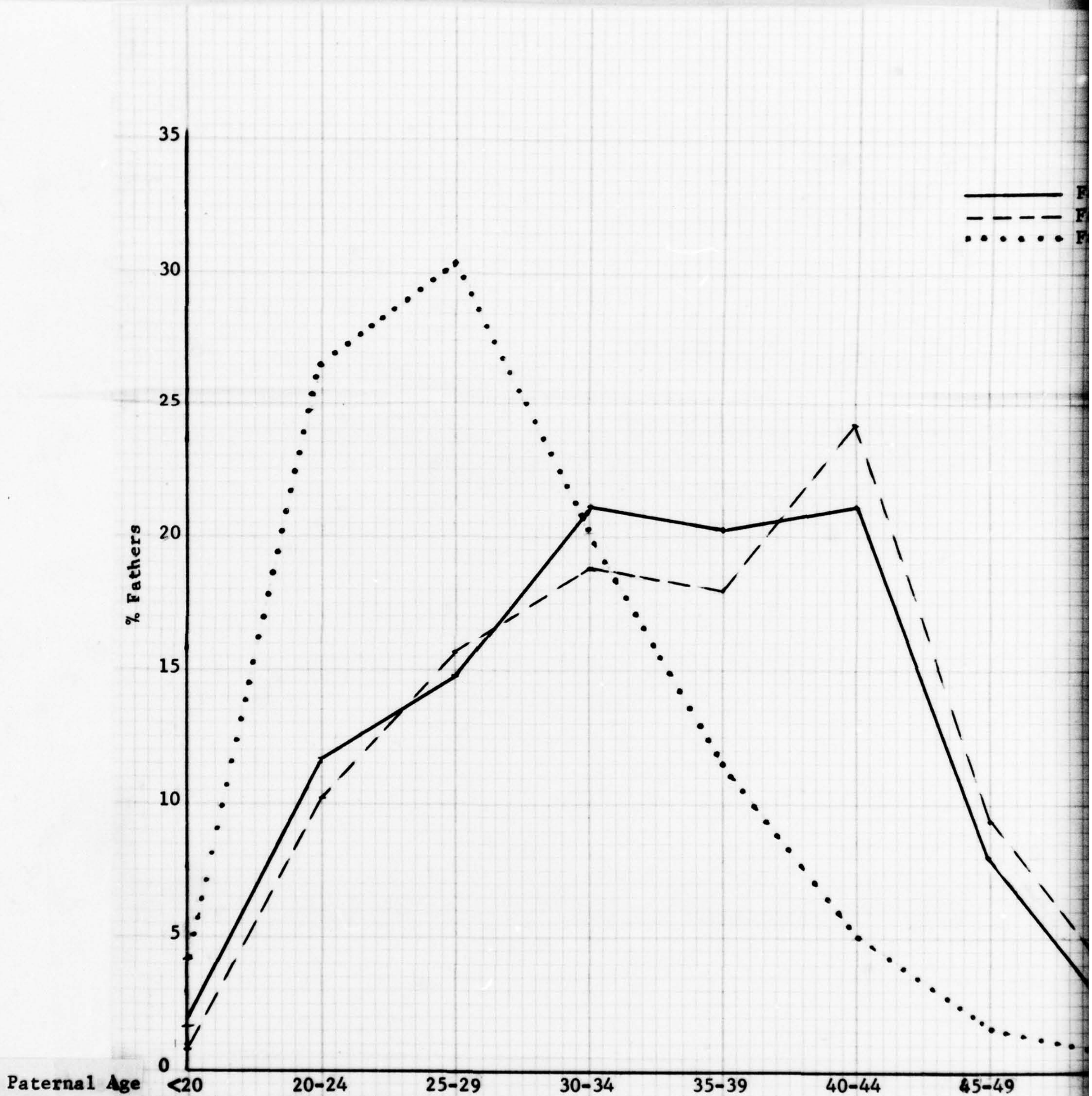
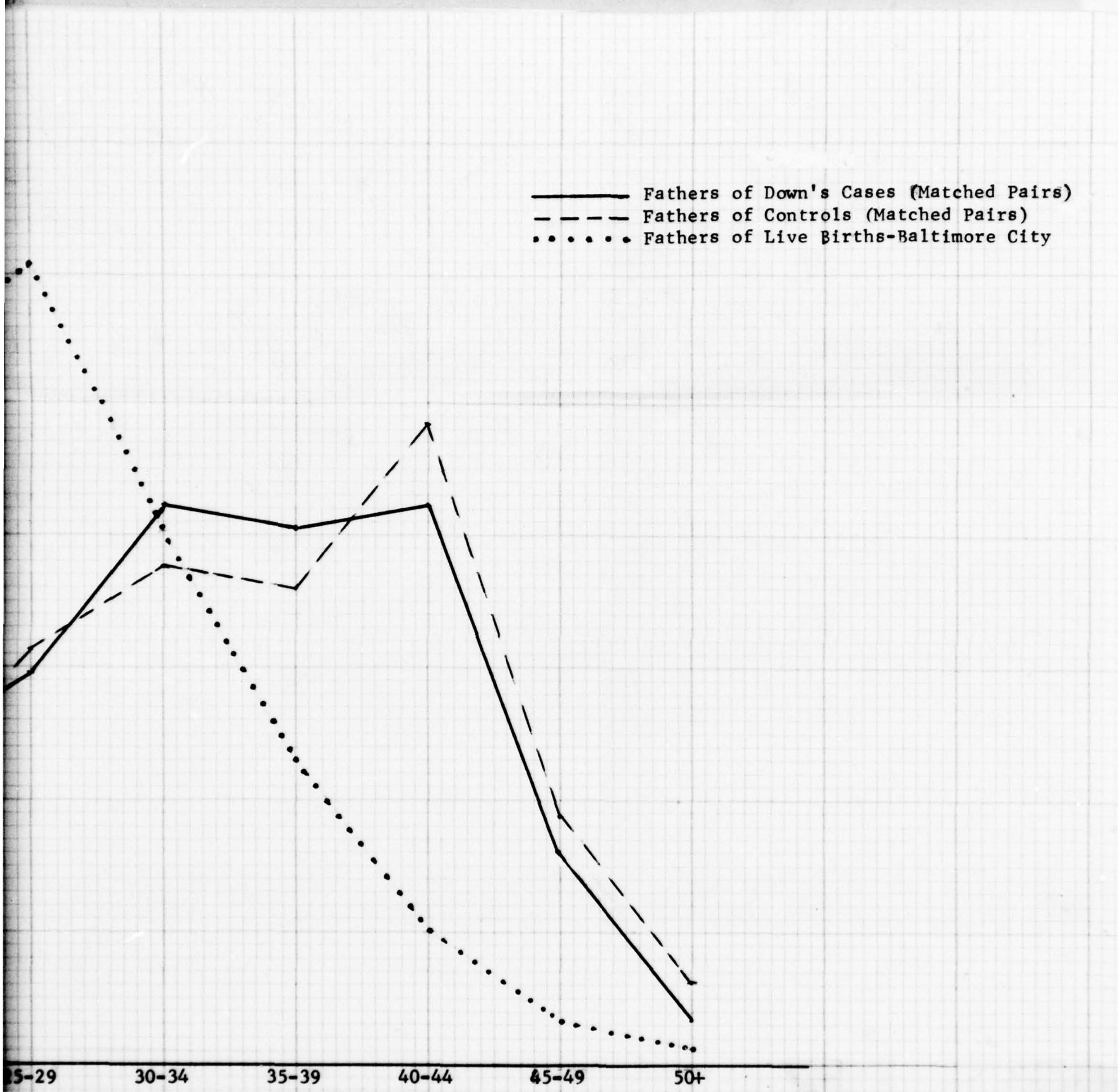


Fig. A-2 Paternal age distributions for Current Series Down's cases and controls (maternal age
Baltimore City.

109 Bottom half



or Current Series Down's cases and controls (maternal age matched) and 1963-1968 white births for

109 Bottom half

2

TABLE R-1

PATERNAL RADAR - MICROWAVE EXPOSURE HISTORY IRRESPECTIVE OF DATE OF CO

Current, Original and Combined Series

Exposure Status	Matched Pairs						
	Down's			Controls			D
	#	% Kn.	% Tot.	#	% Kn.	% Tot.	#
CURRENT SERIES							
No Exposure	39	30.7	30.5	34	26.8	26.6	43
Probably No Exp.	53	41.7	41.4	56	44.1	43.8	66
Probably Some Exp.	13	10.2	10.2	10	7.9	7.8	14
Exposed	22	17.3	17.2	27	21.3	21.1	25
Known Exp. Status	127	99.9	99.3	127	100.1	99.3	148
Unk. Exp. Status	1		0.8	1		0.8	2
Total Incl. Unknown	128		100.1	128		100.1	150
ORIGINAL SERIES							
No Exposure	30	15.4	13.9	25	12.2	11.6	30
Probably No Exp.	116	59.5	53.7	146	71.2	67.6	120
Probably Some Exp.	5	2.6	2.3	1	0.5	0.5	6
Exposed	44	22.6	20.4	33	16.1	15.3	45
Known Exp. Status	195	100.0	90.3	205	100.0	95.0	201
Unk. Exp. Status	21		9.7	11		5.1	21
Total Incl. Unk.	216		100.0	216		100.1	222
COMBINED SERIES							
No Exposure	69	21.4	20.1	59	17.8	17.2	73
Probably No Exp.	169	52.5	49.1	202	60.8	58.7	186
Probably Some Exp.	18	5.6	5.2	11	3.3	3.2	20
Exposed	66	20.5	19.2	60	18.1	17.4	70
Known Exp. Status	322	100.0	93.6	332	100.0	96.5	349
Unk. Exp. Status	22		6.4	12		3.5	23
Total Incl. Unk.	344		100.0	344		100.0	372

+ Includes fathers of additional and questionable Down's cases and fathers of additional co

/AVE EXPOSURE HISTORY IRRESPECTIVE OF DATE OF CONCEPTION (FROM INTERVIEW)

Current, Original and Combined Series

Matched Pairs					Pooled+					
wn's		Controls			Down's			Controls		
.	% Tot.	#	% Kn.	% Tot.	#	% Kn.	% Tot.	#	% Kn.	% Tot.
7	30.5	34	26.8	26.6	43	29.1	28.7	42	29.4	28.0
7	41.4	56	44.1	43.8	66	44.6	44.0	61	42.7	40.7
2	10.2	10	7.9	7.8	14	9.5	9.3	11	7.7	7.3
3	17.2	27	21.3	21.1	25	16.9	16.7	29	20.3	19.3
9	99.3	127	100.1	99.3	148	100.1	98.7	143	100.1	95.3
	0.8	1		0.8	2		1.3	7		4.7
	100.1	128		100.1	150		100.0	150		100.0
	13.9	25	12.2	11.6	30	14.9	13.5	25	12.0	11.3
	53.7	146	71.2	67.6	120	59.7	54.0	148	70.5	67.0
	2.3	1	0.5	0.5	6	3.0	2.7	1	0.5	0.5
	20.4	33	16.1	15.3	45	22.4	20.3	36	17.1	16.3
	90.3	205	100.0	95.0	201	100.0	90.5	210	100.1	95.1
	9.7	11		5.1	21		9.5	11		5.0
	100.0	216		100.1	222		100.0	221		100.1
	20.1	59	17.8	17.2	73	20.9	19.6	67	19.0	18.1
	49.1	202	60.8	58.7	186	53.3	50.0	209	59.2	56.3
	5.2	11	3.3	3.2	20	5.7	5.4	12	3.4	3.2
	19.2	60	18.1	17.4	70	20.1	18.8	65	18.4	17.5
	93.6	332	100.0	96.5	349	100.0	93.8	353	100.0	95.1
	6.4	12		3.5	23		6.2	18		4.9
	100.0	344		100.0	372		100.0	371		100.0

ionable Down's cases and fathers of additional controls, as well as matched pairs.

2

TABLE R-2

PATERNAL RADAR EXPOSURE BEFORE CONCEPTION OF INDEX CHILD (FROM INT

Current, Original, and Combined Series

Exposure Status	Matched Pairs: Down's Cases No.	% Known	% Total	Controls No.	% Known	% Total	Down' No.	% Kn
CURRENT SERIES								
No Exposure Definitely Prior	94	78.3	73.4	91	76.5	71.1	113	80
Probably Some Exposure	16	13.3	12.5	13	10.9	10.2	18	12
Exposed	10	8.3	7.8	15	12.6	11.7	10	7
Known Exposure Status	120	99.9	93.8	119	100.0	93.0	141	100
Unknown Exposure or Time	8		6.2	9		7.0	9	
Total Incl. Unk. Exp. or Time	128		100.0	128		100.0	150	
ORIGINAL SERIES								
No Exposure Definitely Prior	136	81.4	63.0	135	86.5	62.5	140	80
Probably Some Exposure	8	4.8	3.7	3	1.9	1.4	9	5
Exposed	23	13.8	10.6	18	11.5	8.3	24	13
Known Exposure Status	167	100.0	77.3	156	99.9	72.2	173	100
Unknown Exposure or Time	49		22.7	60		27.8	49	
Total Incl. Unk. Exp. or Time	216		100.0	216		100.0	222	
COMBINED SERIES								
No Exposure Definitely Prior	230	80.1	66.9	226	82.2	65.7	253	80
Probably Some Exposure	24	8.3	7.0	16	5.8	4.7	27	8
Exposed	33	11.5	9.6	33	12.0	9.6	34	10
Known Exposure Status	287	99.9	83.4	275	100.0	79.9	314	100
Unknown Exposure or Time	57		16.6	69		20.0	58	
Total Incl. Unk. Exp. or Time	344		100.0	344		99.9	372	

Includes fathers of additional and questionable Down's cases and fathers of additional controls, as

RADAR EXPOSURE BEFORE CONCEPTION OF INDEX CHILD (FROM INTERVIEW)

Current, Original, and Combined Series

Matched Pairs					Pooled #					
n's Cases		Controls			Down's Cases			Controls		
Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total
78.3	73.4	91	76.5	71.1	113	80.1	75.3	106	77.9	70.7
13.3	12.5	13	10.9	10.2	18	12.8	12.0	14	10.3	9.3
8.3	7.8	15	12.6	11.7	10	7.1	6.7	16	11.8	10.7
99.9	93.8	119	100.0	93.0	141	100.0	94.0	136	100.0	90.7
	6.2	9		7.0	9		6.0	14		9.3
	100.0	128		100.0	150		100.0	150		100.0
81.4	63.0	135	86.5	62.5	140	80.9	63.1	137	85.1	62.0
4.8	3.7	3	1.9	1.4	9	5.2	4.1	3	1.9	1.4
13.8	10.6	18	11.5	8.3	24	13.9	10.8	21	13.0	9.5
00.0	77.3	156	99.9	72.2	173	100.0	77.9	161	100.0	72.8
	22.7	60		27.8	49		22.1	60		27.1
	100.0	216		100.0	222		100.0	221		99.9
80.1	66.9	226	82.2	65.7	253	80.6	68.0	243	81.8	65.5
8.3	7.0	16	5.8	4.7	27	8.6	7.3	17	5.7	4.6
11.5	9.6	33	12.0	9.6	34	10.8	9.1	37	12.5	10.0
99.9	83.4	275	100.0	79.9	314	100.0	84.4	297	100.0	80.1
	16.6	69		20.0	58		15.6	74		19.9
	100.0	344		99.9	372		100.0	371		100.0

able Down's cases and fathers of additional controls, as well as matched pairs.

2

TABLE R-3

PATERNAL RADAR EXPOSURE BEFORE CONCEPTION OF INDEX CHILD (FI

Current, Original, and Combined Series

Exposure Status	Matched Pairs							
	Down's Cases			Controls			Down	
	No.	% Known	% Total	No.	% Known	% Total	No.	% K
CURRENT SERIES								
Not Exposed[x]	104	91.2	81.3	104	88.1	81.3	121	9
Exposed	10	8.8	7.8	14	11.9	10.9	12	
Known Exposure Status	114	100.0	89.1	118	100.0	92.2	133	10
Unknown Exposure Status	14		10.9	10		7.8	17	
Total Incl. Unknown Exp.	128		100.0	128		100.0	150	
ORIGINAL SERIES								
Not Exposed[x]	182	89.7	84.3	180	91.8	83.3	185	8
Exposed	21	10.3	9.7	16	8.2	7.4	22	1
Known Exposure Status	203	100.0	94.0	196	100.0	90.7	207	10
Unknown Exposure	13		6.0	20		9.3	15	
Total Incl. Unknown Exp.	216		100.0	216		100.0	222	
COMBINED SERIES								
Not Exposed[x]	286	90.2	83.1	284	90.4	82.6	306	9
Exposed	31	9.8	9.0	30	9.6	8.7	34	1
Known Exposure Status	317	100.0	92.2	314	100.0	91.3	340	10
Unknown Exposure	27		7.8	30		8.7	32	
Total Incl. Unknown Exp.	344		100.0	344		100.0	372	

\# Includes fathers of additional and questionable Down's cases and fathers of additional controls, a

x None reported as definitely prior

AL RADAR EXPOSURE BEFORE CONCEPTION OF INDEX CHILD (FROM NAS)

Current, Original, and Combined Series

	Matched Pairs				Pooled					
Cases		Controls			Down's Cases			Controls		
wn	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total
.2	81.3	104	88.1	81.3	121	91.0	80.7	118	88.7	78.7
.8	7.8	14	11.9	10.9	12	9.0	8.0	15	11.3	10.0
.0	89.1	118	100.0	92.2	133	100.0	88.7	133	100.0	88.7
	10.9	10		7.8	17		11.3	17		11.3
	100.0	128		100.0	150		100.0	150		100.0
.7	84.3	180	91.8	83.3	185	89.4	83.3	183	92.0	82.8
.3	9.7	16	8.2	7.4	22	10.6	9.9	16	8.0	7.2
.0	94.0	196	100.0	90.7	207	100.0	93.2	199	100.0	90.0
	6.0	20		9.3	15		6.8	22		10.0
	100.0	216		100.0	222		100.0	221		100.0
.2	83.1	284	90.4	82.6	306	90.0	82.3	301	90.7	81.1
.8	9.0	30	9.6	8.7	34	10.0	9.1	31	9.3	8.4
.0	92.2	314	100.0	91.3	340	100.0	91.4	332	100.0	89.5
	7.8	30		8.7	32		8.6	39		10.5
	100.0	344		100.0	372		100.0	371		100.0

ble Down's cases and fathers of additional controls, as well as matched pairs.

TABLE R-4

PATERNAL RADAR EXPOSURE BEFORE CONCEPTION OF INDEX CHILD (FROM INTER

Current, Original, and Combined Series

	Matched Pairs							
	Down's Cases			Controls			Dowr	
Exposure Status	No.	% Known	% Total	No.	% Known	% Total	No.	% K
CURRENT SERIES								
No Exp. Definitely Prior x	91	71.7	71.1	91	71.7	71.1	105	7
Probably No Exposure	3	2.4	2.3	0	0	0	5	
Probably Some Exposure	13	10.2	10.2	9	7.1	7.0	14	
Exposed	20	15.7	15.6	27	21.3	21.1	23	1
Known Exposure Status	127	100.0	99.2	127	100.1	99.2	147	9
Unknown Exposure Status	1		0.8	1		0.8	3	
Total Incl. Unknown Exp.	128			128			150	
ORIGINAL SERIES								
No Exp. Definitely Prior x	152	78.4	70.4	166	83.8	76.9	156	
Probably No Exposure	0	0	0	0	0	0	0	
Probably Some Exposure	4	2.1	1.9	1	0.5	0.5	5	
Exposed	38	19.6	17.6	31	15.7	14.4	39	1
Known Exposure Status	194	100.1	89.9	198	100.0	91.8	200	1C
Unknown Exposure Status	22		10.2	18		8.3	22	
Total Incl. Unknown Exp.	216			216			222	
COMBINED SERIES								
No Exp. Definitely Prior x	243	75.7	70.6	257	79.1	74.7	261	7
Probably No Exposure	3	0.9	0.9	0	0	0	5	
Probably Some Exposure	17	5.3	4.9	10	3.1	2.9	19	
Exposed	58	18.1	16.9	58	17.8	16.9	62	1
Known Exposure Status	321	100.0	93.3	325	100.0	94.5	347	1C
Unknown Exposure Status	23		6.7	19		5.5	25	
Total Incl. Unknown Exp.	344			344			372	

Includes fathers of additional and questionable Down's cases and fathers of additional controls, a

x None reported as definitely prior.

DAR EXPOSURE BEFORE CONCEPTION OF INDEX CHILD (FROM INTERVIEW AND/OR NAS)

Current, Original, and Combined Series

Matched Pairs					Pooled[#]					
n's Cases		Controls			Down's Cases			Controls		
Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total
71.7	71.1	91	71.7	71.1	105	71.4	70.0	104	72.7	69.3
2.4	2.3	0	0	0	5	3.4	3.3	0	0	0
10.2	10.2	9	7.1	7.0	14	9.5	9.3	10	7.0	6.7
15.7	15.6	27	21.3	21.1	23	15.6	15.3	29	20.3	19.3
00.0	99.2	127	100.1	99.2	147	99.9	98.0	143	100.0	95.3
	0.8	1		0.8	3		2.0	7		4.7
		128			150			150		
78.4	70.4	166	83.8	76.9	156	78.0	70.3	168	82.8	76.0
0	0	0	0	0	0	0	0	0	0	0
2.1	1.9	1	0.5	0.5	5	2.5	2.3	1	0.5	0.5
19.6	17.6	31	15.7	14.4	39	19.5	17.6	34	16.7	15.4
00.1	89.9	198	100.0	91.8	200	100.0	90.2	203	100.0	91.9
	10.2	18		8.3	22		9.9	18		8.1
		216			222			221		
75.7	70.6	257	79.1	74.7	261	75.2	70.2	272	78.6	73.3
0.9	0.9	0	0	0	5	1.4	1.3	0	0	0
5.3	4.9	10	3.1	2.9	19	5.5	5.1	11	3.2	3.0
18.1	16.9	58	17.8	16.9	62	17.9	16.7	63	18.2	17.0
00.0	93.3	325	100.0	94.5	347	100.0	93.3	346	100.0	93.3
	6.7	19		5.5	25		6.7	25		6.7
		344			372			371		

[#]onable Down's cases and fathers of additional controls, as well as matched pairs.

2

TABLE R-5

TIME OF PATERNAL RADAR EXPOSURE[a] (FROM INTERV

Time of Radar Exposure Relative to Conception	Matched Pairs: Down's Cases No.	Down's Cases % Known	Down's Cases % Total	Controls No.	Controls % Known	Controls % Total
CURRENT SERIES						
None	91	75.8	71.1	90	75.6	70.3
Before	22	18.3	17.2	25	21.0	19.5
Before, During, After	4	3.3	3.1	3	2.5	2.3
After	3	2.5	2.3	1	0.8	0.8
Not Definitely Before[c]	0	0	0	0	0	0
Before and After	0	0	0	0	0	0
Total Known	120	99.9	93.7	119	99.9	93.0
Unknown	8		6.3	9		7.0
Total	128		100.0	128		100.0
ORIGINAL SERIES						
None	129	77.2	59.7	133	85.3	61.6
Before	28	16.8	13.0	18	11.5	8.3
Before, During, After	3	1.8	1.4	2	1.3	0.9
After	6	3.6	2.8	2	1.3	0.9
Not Definitely Before[c]	1	0.6	0.5	0	0	0
Before and After	0	0	0	1	0.6	0.5
Total Known	167	100.0	77.3	156	100.0	72.2
Unknown	49		22.7	60		27.8
Total	216		100.0	216		100.0
COMBINED SERIES						
None	220	76.7	64.0	223	81.1	64.8
Before	50	17.4	14.5	43	15.6	12.5
Before, During, After	7	2.4	2.0	5	1.8	1.5
After	9	3.1	2.6	3	1.1	0.9
Not Definitely Before[c]	1	0.3	0.3	0	0	0
Before and After	0	0	0	1	0.4	0.3
Total Known	287	99.9	83.4	275	100.0	80.0
Unknown	57		16.6	69		20.1
Total	344		100.0	344		100.1

[a] Considered definite and probably some exposure.
[b] Includes fathers of additional and questionable Down's cases and fathers of additional co
[c] Not definitely before - During year of conception, exact date unknown, but not definitely

TIME OF PATERNAL RADAR EXPOSURE[a] (FROM INTERVIEW)

Matched Pairs						Pooled[#]					
Down's Cases			Controls			Down's Cases			Controls		
No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total
91	75.8	71.1	90	75.6	70.3	110	78.0	73.3	105	77.2	70.0
22	18.3	17.2	25	21.0	19.5	24	17.0	16.0	27	19.9	18.0
4	3.3	3.1	3	2.5	2.3	4	2.8	2.7	3	2.2	2.0
3	2.5	2.3	1	0.8	0.8	3	2.1	2.0	1	0.7	0.7
0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0
120	99.9	93.7	119	99.9	93.0	141	99.9	94.0	136	100.0	90.7
8		6.3	9		7.0	9		6.0	14		9.3
128		100.0	128		100.0	150		100.0	150		100.0
129	77.2	59.7	133	85.3	61.6	133	76.9	59.9	135	83.9	61.1
28	16.8	13.0	18	11.5	8.3	30	17.3	13.5	21	13.0	9.5
3	1.8	1.4	2	1.3	0.9	3	1.7	1.4	2	1.2	0.9
6	3.6	2.8	2	1.3	0.9	6	3.5	2.7	2	1.2	0.9
1	0.6	0.5	0	0	0	1	0.6	0.5	0	0	0
0	0	0	1	0.6	0.5	0	0	0	1	0.6	0.5
167	100.0	77.3	156	100.0	72.2	173	100.0	78.0	161	99.9	72.9
49		22.7	60		27.8	49		22.1	60		27.1
216		100.0	216		100.0	222		100.1	221		100.0
220	76.7	64.0	223	81.1	64.8	243	77.4	65.3	240	80.8	64.7
50	17.4	14.5	43	15.6	12.5	54	17.2	14.5	48	16.2	12.9
7	2.4	2.0	5	1.8	1.5	7	2.2	1.9	5	1.7	1.3
9	3.1	2.6	3	1.1	0.9	9	2.9	2.4	3	1.0	0.8
1	0.3	0.3	0	0	0	1	0.3	0.3	0	0	0
0	0	0	1	0.4	0.3	0	0	0	1	0.3	0.3
287	99.9	83.4	275	100.0	80.0	314	100.0	84.4	297	100.0	80.1
57		16.6	69		20.1	58		15.6	74		19.9
344		100.0	344		100.1	372		100.0	371		100.0

exposure.
uestionable Down's cases and fathers of additional controls, as well as matched pairs.
of conception, exact date unknown, but not definitely before conception.

2

TABLE R-6

TIME OF PATERNAL RADAR EXPOSURE□ (FROM NAS)
Current, Original, and Combined Series

	MATCHED PAIRS							
	Down's			Controls			Dow	
TIME OF RADAR EXPOSURE	No.	% Known	% Total	No.	% Known	% Total	No.	% Know
CURRENT SERIES								
None	104	91.2	81.3	104	88.1	81.3	121	91.
Before Conception	10	8.8	7.8	14	11.9	10.9	12	9.
Before-During-After Concep.	0	0	0	0	0	0	0	
After Conception	0	0	0	0	0	0	0	
Not Definitely Before ⊙	0	0	0	0	0	0	0	
Total Known	114	100.0	89.1	118	100.0	92.2	133	100.
Unknown	14		10.9	10		7.8	17	
Total	128		100.0	128		100.0	150	
ORIGINAL SERIES								
None	182	89.7	84.3	180	91.8	83.3	185	89.
Before Conception	20	9.9	9.3	16	8.2	7.4	21	10.
Before-During-After Concep.	1	0.5	0.5	0	0	0	1	0.
After Conception	0	0	0	0	0	0	0	
Not Definitely Before ⊙	0	0	0	0	0	0	0	
Total Known	203	100.0	94.0	196	100.0	90.7	207	100.
Unknown	13		6.0	20		9.3	15	
Total	216		100.0	216		100.0	222	
COMBINED SERIES								
None	286	90.2	83.1	284	90.5	82.6	306	90.
Before Conception	30	9.5	8.7	30	9.6	8.7	33	9.
Before-During-After Concep.	1	0.3	0.3	0	0	0	1	0.
After Conception	0	0	0	0	0	0	0	
Not Definitely Before ⊙	0	0	0	0	0	0	0	
Total Known	317	100.0	92.2	314	100.0	91.3	340	100.
Unknown	27		7.8	30		8.7	32	
Total	344		100.0	344		100.0	372	

□ Considered definitely exposed.
(#) Includes fathers of additional and questionable Down's cases and fathers of additional contr
⊙ Not definitely before - During year of conception, exact date unknown, but not definitely be

TIME OF PATERNAL RADAR EXPOSURE (FROM NAS)

Current, Original, and Combined Series

MATCHED PAIRS					POOLED					
Down's		Controls			Down's			Controls		
% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total
91.2	81.3	104	88.1	81.3	121	91.0	80.7	118	88.7	78.7
8.8	7.8	14	11.9	10.9	12	9.0	8.0	15	11.3	10.0
0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0
100.0	89.1	118	100.0	92.2	133	100.0	88.7	133	100.0	88.7
	10.9	10		7.8	17		11.3	17		11.3
	100.0	128		100.0	150		100.0	150		100.0
89.7	84.3	180	91.8	83.3	185	89.4	83.3	183	92.0	82.8
9.9	9.3	16	8.2	7.4	21	10.1	9.5	16	8.0	7.2
0.5	0.5	0	0	0	1	0.5	0.5	0	0	0
0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0
100.0	94.0	196	100.0	90.7	207	100.0	93.2	199	100.0	90.0
	6.0	20		9.3	15		6.8	22		10.0
	100.0	216		100.0	222		100.0	221		100.0
90.2	83.1	284	90.5	82.6	306	90.0	82.3	301	90.7	81.1
9.5	8.7	30	9.6	8.7	33	9.7	8.9	31	9.3	8.4
0.3	0.3	0	0	0	1	0.0	0.0	0	0	0
0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0
100.0	92.2	314	100.0	91.3	340	100.0	91.4	332	100.0	89.5
	7.8	30		8.7	32		8.6	39		10.5
	100.0	344		100.0	372		100.0	371		100.0

questionable Down's cases and fathers of additional controls, as well as matched pairs.

r of conception, exact date unknown, but not definitely before conception

2

TABLE R-7

PATERNAL RADAR EXPOSURE STATUS BY TIME OF RADAR EXPOSURE (FROM INTERVIEW AND NAS)
Current, Original and Combined Series Matched Pairs

Time Of Exposure Relative To Conception Of Index

PATERNAL EXPOSURE STATUS	NONE		BEFORE		AFTER		NOT DEFINITELY BEFORE ⊙		UNKNOWN		TOTAL	
	Down's	Controls	Down's	Controls	Down's	Controls	Down's	Controls	Down's	Controls	Down's	Controls
CURRENT SERIES												
No Exposure	39	33	0	0	0	0	0	0	0	0	39	33
Probably No Exp.	50	58	3	0	0	0	0	0	0	0	53	58
Probably Some Exp.	0	0	13	9	0	0	0	0	0	0	13	9
Exposed	0	0	20	27	2	0	0	0	0	0	22	27
Known Exp. Status	89	91	36	36	2	0	0	0	0	0	127	127
Unk. Exp. Status	0	0	0	0	0	0	0	0	1	1	1	1
Total Incl. Unk.	89	91	36	36	2	0	0	0	1	1	128	128
ORIGINAL SERIES												
No Exposure	30	26	0	0	0	0	0	0	0	0	30	26
Probably No Exp.	117	138	0	0	0	0	0	0	0	7	117	145
Probably Some Exp.	0	0	4	1	0	0	1	0	1	0	6	1
Exposed	0	0	38	31	3	2	1	0	0	0	42	33
Known Exp. Status	147	164	42	32	3	2	2	0	1	7	195	205
Unk. Exp. Status	0	0	0	0	0	0	0	0	21	11	21	11
Total Incl. Unk.	147	164	42	32	3	2	2	0	22	18	216	216
COMBINED SERIES												
No Exposure	69	59	0	0	0	0	0	0	0	0	69	59
Probably No Exp.	167	196	3	0	0	0	0	0	0	7	170	203
Probably Some Exp.	0	0	17	10	0	0	1	0	1	0	19	10
Exposed	0	0	58	58	5	2	1	0	0	0	64	60
Known Exp. Status	236	255	78	68	5	2	2	0	1	7	322	332
Unk. Exp. Status	0	0	0	0	0	0	0	0	22	12	22	12
Total Incl. Unk.	236	255	78	68	5	2	2	0	23	19	344	344

⊙ Not definitely before = During year of conception, exact date unknown, but not definitely before conception.

TABLE R-8

PATERNAL RADAR EXPOSURE STATUS BY TIME OF RADAR EXPOSURE (FROM INTERVIEW AND/OR NAS)
Current, Original, and Combined Series Pooled (#)

RADAR EXPOSURE SUMMARY	NONE		BEFORE		AFTER		NOT DEFINITELY BEFORE (·)		UNKNOWN		TOTAL	
	Down's	Controls	Down's	Controls	Down's	Controls	Down's	Controls	Down's	Controls	Down's	Controls
CURRENT SERIES												
No Exposure	43	41	0	0	0	0	0	0	0	0	43	41
Probably No Exp.	60	63	5	0	0	0	0	0	1	0	66	63
Probably Some Exp.	0	0	14	10	0	0	0	0	0	0	14	10
Exposed	0	0	23	29	2	0	0	0	0	0	25	29
Unk. Exp. Status	0	0	0	0	0	0	0	0	2	7	2	7
Total Incl. Unk.	103	104	42	39	2	0	0	0	3	7	150	150
Known Exp. Status	103	104	42	39	2	0	0	0	1	0	148	143
ORIGINAL SERIES												
No Exposure	30	26	0	0	0	0	0	0	0	0	30	26
Probably No Exp.	121	140	0	0	0	0	0	0	0	7	121	147
Probably Some Exp.	0	0	5	1	0	0	1	0	1	0	7	1
Exposed	2	1	37	33	3	2	1	0	0	0	43	36
Unk. Exp. Status	0	0	0	0	0	0	0	0	21	11	21	11
Total Incl. Unk.	153	167	42	34	3	2	2	0	22	18	222	221
Known Exp. Status	153	167	42	34	3	2	2	0	1	7	201	210
COMBINED SERIES												
No Exposure	73	67	0	0	0	0	0	0	0	0	73	67
Probably No Exp.	181	203	5	0	0	0	0	0	1	7	187	210
Probably Some Exp.	0	0	19	11	0	0	1	0	1	0	21	11
Exposed	2	1	60	62	5	2	1	0	0	0	68	65
Unk. Exp. Status	0	0	0	0	0	0	0	0	23	18	23	18
Total Incl. Unk.	256	271	84	73	5	2	2	0	25	25	372	371
Known Exp. Status	256	271	84	73	5	2	2	0	2	7	349	353

(#) Includes fathers of additional and questionable Down's and fathers of additional controls, as well as matched pairs.
(·) Not definitely before = During year of conception, exact date unknown, but not definitely before conception.

TABLE R-9

PATERNAL HISTORY OF MILITARY SERVICE ON SHIPBOARD (FROM INTERVIEW)

Time Relative to Index Conception	Matched Pairs						Pooled #					
	Down's			Controls			Down's			Controls		
	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total
CURRENT SERIES												
Prior												
Above Deck	14	11.2	10.9	21	17.2	16.4	16	11.0	10.7	23	16.5	15.3
Below Deck	10	8.0	7.8	7	5.7	5.5	11	7.5	7.3	9	6.5	6.0
Other Times Only												
Above Deck	0	0	0	0	0	0	0	0	0	0	0	0
Below Deck	1	0.8	0.8	0	0	0	1	0.7	0.7	0	0	0
No Service on Ship	100	80.0	78.1	94	77.0	73.4	118	80.0	78.7	107	77.0	71.3
Total Known	125		97.7	122		95.3	146		97.3	139		92.7
Unknown Time												
Above Deck	0		0	1		0.8	0		0	1		0.7
Below Deck	0		0	0		0	0		0	0		0
Unknown	3		2.3	5		3.9	4		2.7	10		6.7
Total	128			128			150			150		
ORIGINAL SERIES												
Prior												
Above Deck	14	9.1	6.5	18	10.9	8.3						
Below Deck	5	3.2	2.3	5	3.0	2.3						
Other Times Only												
Above Deck	0	0	0	0	0	0						
Below Deck	0	0	0	1	0.6	0.5						
No Service on Ship	135	87.7	62.5	141	85.5	65.3						
Total Known	154		71.3	165		76.4						
Unknown Time												
Above Deck	0		0	0		0						
Below Deck	0		0	0		0						
Unknown	62		28.7	51		23.6						
Total	216			216								
COMBINED SERIES												
Prior												
Above Deck	28	10.0	8.1	39	13.6	11.3						
Below Deck	15	5.4	4.4	12	4.2	3.5						
Other Times Only												
Above Deck	0	0	0	1	0.3	0.3						
Below Deck	1	0.4	0.3	0	0	0						
No Service on Ship	235	84.2	68.3	235	81.9	68.3						
Total Known	279		81.1	287		83.4						

TABLE R-9

PATERNAL HISTORY OF MILITARY SERVICE ON SHIPBOARD (FROM INTERVI

Time Relative to Index Conception	Matched Pairs						Po		
	Down's			Controls			Down's		
	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Tot
CURRENT SERIES									
Prior									
Above Deck	14	11.2	10.9	21	17.2	16.4	16	11.0	10.7
Below Deck	10	8.0	7.8	7	5.7	5.5	11	7.5	7.3
Other Times Only									
Above Deck	0	0	0	0	0	0	0	0	0
Below Deck	1	0.8	0.8	0	0	0	1	0.7	0.7
No Service on Ship ⊙	100	80.0	78.1	94	77.0	73.4	118	80.0	78.7
Total Known	125		97.7	122		95.3	146		97.3
Unknown Time									
Above Deck	0		0	1		0.8	0		0
Below Deck	0		0	0		0	0		0
Unknown	3		2.3	5		3.9	4		2.7
Total	128			128			150		
ORIGINAL SERIES									
Prior									
Above Deck	14	9.1	6.5	18	10.9	8.3			
Below Deck	5	3.2	2.3	5	3.0	2.3			
Other Times Only									
Above Deck	0	0	0	0	0	0			
Below Deck	0	0	0	1	0.6	0.5			
No Service on Ship ⊙	135	87.7	62.5	141	85.5	65.3			
Total Known	154		71.3	165		76.4			
Unknown Time									
Above Deck	0		0	0		0			
Below Deck	0		0	0		0			
Unknown	62		28.7	51		23.6			
Total	216			216					
COMBINED SERIES									
Prior									
Above Deck	28	10.0	8.1	39	13.6	11.3			
Below Deck	15	5.4	4.4	12	4.2	3.5			
Other Times Only									
Above Deck	0	0	0	1	0.3	0.3			
Below Deck	1	0.4	0.3	0	0	0			
No Service on Ship ⊙	235	84.2	68.3	235	81.9	68.3			
Total Known	**279**		**81.1**	**287**		**83.4**			
Unknown Time	0								
Above Deck	0		0		1	0.3			
Below Deck	0		0		0	0			
Unknown	65		18.9		56	16.3			
Total	344				344				

⊙ Includes those with no reported military service

(#) Includes fathers of additional and questionable Down's cases and fathers of additional controls

NOTE: Time of radar exposure referred to as "before","after","prior", etc. refers to time relative t child in all tabulations.

ATERNAL HISTORY OF MILITARY SERVICE ON SHIPBOARD (FROM INTERVIEW)

Matched Pairs					Pooled					
wn's		Controls			Down's			Controls		
Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total
.2	10.9	21	17.2	16.4	16	11.0	10.7	23	16.5	15.3
.0	7.8	7	5.7	5.5	11	7.5	7.3	9	6.5	6.0
	0	0	0	0	0	0	0	0	0	0
.8	0.8	0	0	0	1	0.7	0.7	0	0	0
.0	78.1	94	77.0	73.4	118	80.0	78.7	107	77.0	71.3
	97.7	122		95.3	146		97.3	139		92.7
	0	1		0.8	0		0	1		0.7
	0	0		0	0		0	0		0
	2.3	5		3.9	4		2.7	10		6.7
		128			150			150		
.1	6.5	18	10.9	8.3						
.2	2.3	5	3.0	2.3						
	0	0	0	0						
	0	1	0.6	0.5						
.7	62.5	141	85.5	65.3						
	71.3	165		76.4						
	0	0		0						
	0	0		0						
	28.7	51		23.6						
		216								
.0	8.1	39	13.6	11.3						
.4	4.4	12	4.2	3.5						
	0	1	0.3	0.3						
.4	0.3	0	0	0						
.2	68.3	235	81.9	68.3						
	81.1	287		83.4						
	0		1	0.3						
	0		0	0						
	18.9		56	16.3						
			344							

litary service

questionable Down's cases and fathers of additional controls, as well as matched pairs.

to as "before","after","prior", etc.refers to time relative to conception of index

TABLE R-10

PATERNAL HISTORY OF WORK WITH RADAR I
Matched Pairs of Current, Or
Pooled Fathers of

SERIES Time Relative to Index Conception	Repair						Maintain								
	Cases			Controls			Cases			Controls			Cases		
	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	To
MATCHED PAIRS															
CURRENT SERIES															
Prior	3	2.4	2.3	6	4.9	4.7	3	2.4	2.3	5	4.1	3.9	7	5.6	5.
Other Times Only	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
None	121	97.6	94.5	117	95.1	91.4	121	97.6	94.5	118	95.9	92.2	117	94.4	91.
Total Known	124		96.9	123		96.1	124		96.9	123		96.1	124		96.
Unknown	4		3.1	5		3.9	4		3.1	5		3.9	4		3.
Total	128			128			128			128			128		
ORIGINAL SERIES															
Prior	5	2.5	2.3	1	0.5	0.5	6	3.0	2.8	2	1.0	0.9	8	4.0	3.
Other Times Only	1	0.5	0.5	0	0	0	1	0.5	0.5	0	0	0	1	0.5	0.
None	192	97.0	88.9	209	99.5	96.8	191	96.5	88.4	208	99.0	96.3	191	95.5	88.
Total Known	198		91.7	210		97.2	198		91.7	210		97.2	200		92.
Unknown	18		8.3	6		2.8	18		8.3	6		2.8	16		7.
Total	216			216			216			216			216		
COMBINED SERIES															
Prior	8	2.5	2.3	7	2.1	2.0	9	2.8	2.6	7	2.1	2.0	15	4.6	4.
Other Times Only	1	0.3	0.3	0	0	0	1	0.3	0.3	0	0	0	1	0.3	0.
None	313	97.2	91.0	326	97.9	94.8	312	96.9	90.7	326	97.9	94.8	308	95.1	89.
Total Known	322		93.6	333		96.8	322		93.6	333		96.8	324		94.
Unknown	22		6.4	11		3.2	22		6.4	11		3.2	20		5.
Total	344			344			344			344			344		
POOLED FATHERS															
CURRENT SERIES															
Prior	3	2.1	2.0	6	4.3	4.0	3	2.1	2.0	5	3.6	3.3	7	4.8	4.
Other Times Only	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
None	142	97.9	94.7	134	95.7	89.3	142	97.9	94.7	135	96.4	90.0	138	95.2	92.
Total Known	145		96.7	140		93.3	145		96.7	140		93.3	145		96.
Unknown	5		3.3	10		6.7	5		33.3	10		6.7	5		3.
Total	150			150			150			150			150		

⊙ Includes those with no reported military service.
⊗ Includes those with exact type of work undefined.
(#) Includes fathers of additional and questionable Down's cases and fathers of additional controls, a

WORK WITH RADAR IN MILITARY SERVICE (FROM INTERVIEW)
airs of Current, Original, and Combined Series
Pooled Fathers of Current Series

	Operate						Test						Other Work					
ols	Cases			Controls			Cases			Controls			Cases			Controls		
% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total
3.9	7	5.6	5.5	11	8.9	8.6	5	4.0	3.9	6	4.9	4.7	2	1.6	1.6	0	0	0
0	0	0	0	0	0	0	1	0.8	0.8	0	0	0	0	0	0	0	0	0
2.2	117	94.4	91.4	112	91.1	87.5	118	95.2	92.2	117	95.1	91.4	122	98.4	95.3	123	100.0	96.1
6.1	124		96.9	123		96.1	124		96.9	123		96.1	124		96.9	123		96.1
3.9	4		3.1	5		3.9	4		3.1	5		3.9	4		3.1	5		3.9
	128			128			128			128			128			128		
0.9	8	4.0	3.7	7	3.3	3.2	5	2.5	2.3	1	0.5	0.5	5	2.5	2.3	1	0.5	0.5
0	1	0.5	0.5	2	1.0	0.9	1	0.5	0.5	0	0	0	1	0.5	0.5	0	0	0
6.3	191	95.5	88.4	201	95.7	93.1	192	97.0	88.9	209	99.5	96.8	194	97.0	89.8	209	99.5	96.8
7.2	200		92.6	210		97.2	198		91.7	210		97.2	200		92.6	210		97.2
2.8	16		7.4	6		2.8	18		8.3	6		2.8	16		7.4	6		2.8
	216			216			216			216			216			216		
2.0	15	4.6	4.4	18	5.4	5.2	10	3.1	2.9	7	2.1	2.0	7	2.2	2.0	1	0.3	0.3
	1	0.3	0.3	2	0.6	0.6	2	0.6	0.6	0	0	0	1	0.3	0.3	0	0	0
.8	308	95.1	89.5	313	94.0	91.0	310	96.3	90.1	326	97.9	94.8	316	97.5	91.9	332	99.7	96.5
.8	324		94.2	333		96.8	322		93.6	333		96.8	324		94.2	333		96.8
.2	20		5.8	11		3.2	22		6.4	11		3.2	20		5.8	11		3.2
	344			344			344			344			344			344		
.3	7	4.8	4.7	12	8.6	8.0	5	3.4	3.3	6	4.3	4.0	2	1.4	1.3	0	0	0
	0	0	0	0	0	0	1	0.7	0.7	0	0	0	0	0	0	0	0	0
.0	138	95.2	92.0	128	91.4	85.3	139	95.9	92.7	134	95.7	89.3	143	98.6	95.3	140	100.0	93.3
.3	145		96.7	140		93.3	145		96.7	140		93.3	145		96.7	140		93.3
.7	5		3.3	10		6.7	5		3.3	10		6.7	5		3.3	10		6.7
	150			150			150			150			150			150		

tional controls, as well as matched pairs.

TABLE R-11

PATERNAL HISTORY OF WORK WITH MICROWAVE IN

SERIES Time Relative to Index Conception	Repair						Maintain							
	Cases			Controls			Cases			Controls			Cases	
	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known
MATCHED PAIRS														
CURRENT SERIES														
Prior	1	0.8	0.8	2	1.6	1.6	1	0.8	0.8	1	0.8	0.8	2	1.6
Other Times Only	0	0	0	0	0	0	0	0	0	0	0	0	0	0
None	122	99.2	95.3	121	98.4	94.5	122	99.2	95.3	122	99.2	95.3	121	98.4
Total Known	123		96.1	123		96.1	123		96.1	123		96.1	123	
Unknown	5		3.9	5		3.9	5		3.9	5		3.9	5	
Total	128			128			128			128			128	
ORIGINAL SERIES														
Prior	4	2.0	1.9	1	0.5	0.5	4	2.0	1.9	1	0.5	0.5	3	1.5
Other Times Only	0	0	0	0	0	0	0	0	0	0	0	0	0	0
None	194	98.0	89.8	207	99.5	95.8	194	98.0	89.8	207	99.5	95.8	195	98.5
Total Known	198		91.7	208		96.3	198		91.7	208		96.3	198	
Unknown	18		8.3	8		3.7	18		8.3	8		3.7	18	
Total	216			216			216			216			216	
COMBINED SERIES														
Prior	5	1.6	1.4	3	0.9	0.9	5	1.6	1.4	2	0.6	0.6	5	1.6
Other Times Only	0	0	0	0	0	0	0	0	0	0	0	0	0	0
None	316	98.4	91.9	328	99.1	95.4	316	98.4	91.9	329	99.4	95.6	316	98.4
Total Known	321		93.3	331		96.2	321		93.3	331		96.2	321	
Unknown	23		6.7	13		3.8	23		6.7	13		3.8	23	
Total	344			344			344			344			344	
POOLED FATHERS #														
CURRENT SERIES														
Prior	1	0.7	0.7	2	1.4	1.3	1	0.7	0.7	1	0.7	0.7	2	1.4
Other Times Only	0	0	0	0	0	0	0	0	0	0	0	0	0	0
None	43	99.3	95.3	138	98.6	92.0	143	99.3	95.3	139	99.3	92.7	142	98.6
Total Known	144		96.0	140		93.3	144		96.0	140		93.3	144	
Unknown	6		4.0	10		6.7	6		4.0	10		6.7	6	
Total	150			150			150			150			150	

⊙ Includes those with no reported military service.
⊗ Includes those with exact type of work undefined.
\# Includes fathers of additional and questionable Down's cases and fathers of additional controls,

ITH MICROWAVE IN MILITARY SERVICE (FROM INTERVIEW)

ls	Operate						Test						Other Work					
	Cases			Controls			Cases			Controls			Cases			Controls		
% otal	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total
0.8	2	1.6	1.6	0	0	0	2	1.6	1.6	1	0.8	0.8	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
95.3	121	98.4	94.5	123	100.0	96.1	121	98.4	94.5	122	99.2	95.3	123	100.0	96.1	123	100.0	96.1
96.1	123		96.1	123		96.1	123		96.1	123		96.1	123		96.1	123		96.1
3.9	5		3.9	5		3.9	5		3.9	5		3.9	5		3.9	5		3.9
	128			128			128			128			128			128		
0.5	3	1.5	1.4	1	0.5	0.5	3	1.5	1.4	0	0	0	2	1.0	0.9	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
95.8	195	98.5	90.3	206	99.5	95.4	195	98.5	90.3	208	100.0	96.3	196	99.0	90.7	207	100.0	96.3
96.3	198		91.7	207		95.8	198		91.7	208		96.3	198		91.7	207		96.3
3.7	18		8.3	9		4.2	18		8.3	8		3.7	18		8.3	9		3.7
	216			216			216			216			216			216		
0.6	5	1.6	1.4	1	0.3	0.3	5	1.6	1.4	1	0.3	0.3	2	0.6	0.6	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
95.6	316	98.4	91.9	329	99.7	95.6	316	98.4	91.9	330	99.7	95.9	319	99.4	92.7	330	100.0	95.9
96.2	321		93.3	330		95.9	321		93.3	331		96.2	321		93.3	330		95.9
3.8	23		6.7	14		4.1	23		6.7	13		3.8	23		6.7	14		4.1
	344			344			344			344			344			344		
0.7	2	1.4	1.3	0	0	0	2	1.4	1.3	1	0.7	0.7	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
92.7	142	98.6	94.7	140	100.0	93.3	142	98.6	94.7	139	99.3	92.7	144	100.0	96.0	140	100.0	93.3
93.3	144		96.0	140		93.3	144		96.0	140		93.3	144		96.0	140		93.3
6.7	6		4.0	10		6.7	6		4.0	10		6.7	6		4.0	10		6.7
	150			150			150			150			150			150		

ional controls, as well as matched pairs.

TABLE R-12

PATERNAL HISTORY OF WORK WITH ELECTRONIC P

SERIES Time Relative to Index Conception	Repair						Maintain						C	
	Cases			Controls			Cases			Controls				
MATCHED PAIRS	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	Kn
CURRENT SERIES														
Prior	5 ⊗	4.2	3.9	6 ⊗	4.9	4.7	4 ⊗	3.3	3.1	6 ⊗	4.9	4.7	4 ⊗	
Other Times Only	0	0	0	0	0	0	0	0	0	0	0	0	0	
None ⊙	115	95.8	89.8	117	95.1	91.4	116	96.7	90.6	117	95.1	91.4	116	9
Total Known	120		93.8	123		96.1	120		93.8	123		96.1	120	
Unknown	8		6.2	5		3.9	8		6.2	5		3.9	8	
Total	128			128			128			128			128	
ORIGINAL SERIES														
Prior	6 ⊗	5.8	2.8	1	0.8	0.4	7 ⊗	6.7	3.2	3	2.4	1.4	7 ⊗	
Other Times Only	0	0	0	0	0	0	0	0	0	0	0	0	0	
None ⊙	98	94.2	45.3	125	99.2	57.9	97	93.3	44.9	123	97.6	56.9	97	9
Total Known	104		48.1	126		58.3	104		48.1	126		58.3	104	
Unknown	112		51.9	90		41.7	112		51.9	90		41.7	112	
Total	216			216			216			216			216	
COMBINED SERIES														
Prior	11 ⊗	4.9	3.2	7 ⊗	2.8	2.0	11 ⊗	4.9	3.2	9 ⊗	3.6	2.6	11 ⊗	
Other Times Only	0	0	0	0	0	0	0	0	0	0	0	0	0	
None	213	95.1	61.9	242	97.2	70.3	213	95.1	61.9	240	96.4	69.8	213	9
Total Known	224		65.1	249		72.4	224		65.1	249		72.4	224	
Unknown	120		34.9	95		27.6	120		34.9	95		27.6	120	
Total	344			344			344			344			344	
POOLED FATHERS (#)														
CURRENT SERIES														
Prior	6 ⊗	4.3	4.0	6 ⊗	4.3	4.0	4	2.8	2.7	6 ⊗	4.3	4.0	4 ⊗	
Other Times Only	0	0	0	0	0	0	0	0	0	0	0	0	0	
None ⊙	135	95.7	90.0	134	95.7	89.3	137	97.2	91.3	134	95.7	89.3	137	9
Total Known	141		94.0	140		93.3	141		94.0	140		93.3	141	
Unknown	9		6.0	10		6.7	9		6.0	10		6.7	9	
Total	150			150			150			150			150	

⊙ Includes those with no reported military service.
⊗ Includes those with exact type of work undefined.
(#) Includes fathers of additional and questionable Down's cases and fathers of additional contro

TRONIC PRODUCTS IN MILITARY SERVICE (FROM INTERVIEW)

Operate						Test						Other Work					
Cases			Controls			Cases			Controls			Cases			Controls		
No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total
4	3.3	3.1	9	7.3	7.0	2	1.7	1.6	6	4.9	4.7	1	0.8	0.8	1	0.8	0.8
0	0	0	0	0	0	0	0	0	1	0.8	0.8	0	0	0	0	0	0
116	96.7	90.6	114	93.7	89.1	118	98.3	92.2	116	94.3	90.6	119	99.2	93.0	122	99.2	95.3
120		93.8	123		96.1	120		93.8	123		96.1	120		93.8	123		96.1
8		6.2	5		3.9	8		6.2	5		3.9	8		6.2	5		3.9
128			128			128			128			128			128		
7	6.7	3.2	5	4.0	2.3	4	3.8	1.9	1	0.8	0.4	3	2.9	1.4	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
97	93.3	44.9	121	96.0	56.0	100	96.2	46.3	125	99.2	57.9	101	97.1	46.8	126	100.0	58.3
104		48.1	126		58.3	104		48.1	126		58.3	104		48.1	126		58.3
112		51.9	90		41.7	112		51.9	90		41.7	112		51.9	90		41.7
216			216			216			216			216			216		
11	4.9	3.2	14	5.6	4.1	6	2.7	1.7	7	2.8	2.0	4	1.8	1.2	1	0.4	0.3
0	0	0	0	0	0	0	0	0	1	0.4	0.3	0	0	0	0	0	0
213	95.1	61.9	235	94.4	68.3	218	97.3	63.4	241	96.8	70.1	220	98.2	64.0	248	99.6	72.1
224		65.1	249		72.4	224		65.1	249		72.4	224		65.1	249		72.4
120		34.9	95		27.6	120		34.9	95		27.6	120		34.9	95		27.6
344			344			344			344			344			344		
4	2.8	2.7	9	6.4	6.0	2	1.4	1.3	6	4.3	4.0	1	0.7	0.7	1	0.7	0.7
0	0	0	0	0	0	0	0	0	1	0.7	0.7	0	0	0	0	0	0
137	97.2	91.3	131	93.6	87.3	139	98.6	92.7	133	95.0	88.7	140	99.3	93.3	139	99.3	92.7
141		94.0	140		93.3	141		94.0	140		93.3	141		94.0	140		93.3
9		6.0	10		6.7	9		6.0	10		6.7	9		6.0	10		6.7
150			150			150			150			150			150		

l controls, as well as matched pairs.

TABLE R-13

PATERNAL HISTORY OF WORK WITH RADIO COMMU

SERIES Time Relative to Index Conception	Repair						Maintain						
	Cases			Controls			Cases			Controls			Case
	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known
MATCHED PAIRS														
CURRENT SERIES														
Prior	10 ⊗	8.1	7.8	5	4.1	3.9	12 x	9.8	9.4	5	4.1	3.9	20 ⊗	16.3
Other Times Only	0	0	0	0	0	0	0	0	0	0	0	0	1	0.8
None ⊙	113	91.9	88.3	118	95.9	92.2	111	90.2	86.7	118	95.9	92.2	102	82.9
Total Known	123		96.1	123		96.1	123		96.1	123		96.1	123	
Unknown	5		3.9	5		3.9	5		3.9	5		3.9	5	
Total	128			128			128			128			128	
ORIGINAL SERIES														
Prior	8 ⊗	5.4	3.7	4 ⊗	2.5	1.8	10 ⊗	6.8	4.6	5 ⊗	3.1	2.3	13 ⊗	8.7
Other Times Only	1	0.7	0.5	0	0	0	1	0.7	0.5	0	0	0	1	0.7
None ⊙	139	93.9	64.4	158	97.5	73.2	137	92.6	63.4	157	96.9	72.7	135	90.6
Total Known	148		68.5	162		75.0	148		68.5	162		75.0	149	
Unknown	68		31.5	54		25.0	68		31.5	54		25.0	67	
Total	216			216			216			216			216	
COMBINED SERIES														
Prior	18 ⊗	6.6	5.2	9 ⊗	3.2	2.6	22 ⊗	8.1	6.4	10 ⊗	3.5	2.9	33 x	12.1
Other Times Only	1	0.4	0.3	0	0	0	1	0.4	0.3	0	0	0	2	0.8
None	252	93.0	73.3	276	96.8	80.2	248	91.5	72.1	275	96.5	79.9	237	87.1
Total Known	271		78.8	285		82.8	271		78.8	285		82.8	272	
Unknown	73		21.2	59		17.2	73		21.2	59		17.2	72	
Total	344			344			344			344			344	
POOLED FATHERS (#)														
CURRENT SERIES														
Prior	11 ⊗	7.6	7.3	5	3.6	3.3	12 ⊗	8.3	8.0	5	3.6	3.3	21 ⊗	14.6
Other Times Only	0	0	0	0	0	0	0	0	0	0	0	0	1	0.7
None ⊙	133	92.4	88.7	135	96.4	90.0	132	91.7	88.0	135	96.4	90.0	122	84.7
Total Known	144		96.0	140		93.3	144		96.0	140		93.3	144	
Unknown	6		4.0	10		6.7	6		4.0	10		6.7	6	
Total	150			150			150			150			150	

⊙ Includes those with no reported military service.
⊗ Includes those with exact type of work undefined.
(#) Includes fathers of additional and questionable Down's cases and fathers of additional controls,

ITH RADIO COMMUNICATIONS GEAR IN MILITARY SERVICE (FROM INTERVIEW)

ls	Operate						Test						Other Work					
	Cases			Controls			Cases			Controls			Cases			Controls		
% otal	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total
3.9	20	16.3	15.6	13	10.6	10.2	7	5.7	5.5	3	2.4	2.3	0	0	0	0	0	0
0	1	0.8	0.8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
92.2	102	82.9	79.7	110	89.4	85.9	116	94.3	90.6	120	97.6	93.8	123	100.0	96.1	123	100.0	96.1
96.1	123		96.1	123		96.1	123		96.1	123		96.1	123		96.1	123		96.1
3.9	5		3.9	5		3.9	5		3.9	5		3.9	5		3.9	5		3.9
	128			128			128			128			128			128		
2.3	13	8.7	6.0	10	6.2	4.6	5	3.4	2.3	3	1.9	1.4	3	2.0	1.4	3	1.9	1.4
0	1	0.7	0.5	0	0	0	1	0.7	0.5	0	0	0	0	0	0	0	0	0
72.7	135	90.6	62.5	152	93.8	70.4	142	95.9	65.7	159	98.1	73.6	146	98.0	67.6	159	98.1	73.6
75.0	149		69.0	162		75.0	148		68.5	162		75.0	149		69.0	162		75.0
25.0	67		31.0	54		25.0	68		31.5	54		25.0	67		31.0	54		25.0
	216			216			216			216			216			216		
2.9	33	12.1	9.6	23	8.1	6.7	12	4.4	3.5	6	2.1	1.7	3	1.1	0.9	3	1.1	0.9
0	2	0.8	0.6	0	0	0	1	0.4	0.3	0	0	0	0	0	0	0	0	0
79.9	237	87.1	68.9	262	91.9	76.2	258	95.2	75.0	279	97.9	81.1	269	98.9	78.2	282	98.9	82.0
82.8	272		79.1	285		82.8	271		78.8	285		82.8	272		79.1	285		82.8
17.2	72		20.9	59		17.2	73		21.2	59		17.2	72		20.9	59		17.2
	344			344			344			344			344			344		
3.3	21	14.6	14.0	13	9.3	8.7	7	4.9	4.7	3	2.1	2.0	0	0	0	0	0	0
0	1	0.7	0.7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
90.0	122	84.7	81.3	127	90.7	84.7	137	95.1	91.3	137	97.9	91.3	144	100.0	96.0	140	100.0	93.3
93.3	144		96.0	140		93.3	144		96.0	140		93.3	144		96.0	140		93.3
6.7	6		4.0	10		6.7	6		4.0	10		6.7	6		4.0	10		6.7
	150			150			150			150			150			150		

onal controls, as well as matched pairs.

TABLE R-14 PATERNAL HISTORY OF WORK INVOLVING SPECIAL SITES AND/OR EQUIPMENT IN MILITARY S

	Ever stationed at air field?						Ever stationed at radar park?						Ev		
	Down's			Controls			Down's			Controls			Down's		
	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	To
MATCHED PAIRS															
CURRENT SERIES															
Yes	26	21.1	20.3	23	18.7	18.0	8	6.6	6.3	7	5.8	5.5	5	4.0	3
No ⊙	97	78.9	75.7	100	81.3	78.1	114	93.4	89.1	114	94.2	89.1	119	96.0	93
Total Known	123		96.1	123		96.1	122		95.3	121		94.5	124		96
Unknown	5		3.9	5		3.9	6		4.7	7		5.5	4		3
Total	128			128			128			128			128		
ORIGINAL SERIES															
Yes	24	15.7	11.1	22	13.8	10.2	7	4.8	3.2	3	1.9	1.4	0	0	0
No ⊙	129	84.3	59.7	138	86.2	63.9	140	95.2	64.8	157	98.1	72.7	153	100.0	70
Total Known	153		70.8	160		74.1	147		68.1	160		74.1	153		70
Unknown	63		29.2	56		25.9	69		31.9	56		25.9	63		29
Total	216			216			216			216			216		
COMBINED SERIES															
Yes	50	18.1	14.5	45	15.9	13.1	15	5.6	4.4	10	3.6	2.9	5	1.8	1
No ⊙	226	81.9	65.7	238	84.1	69.2	254	94.4	73.8	271	96.4	78.8	272	98.2	79
Total Known	276		80.2	283		82.3	269		78.2	281		81.7	277		80
Unknown	68		19.8	61		17.7	75		21.8	63		18.3	67		19
Total	344			344			344			344			344		
POOLED FATHERS #															
CURRENT SERIES															
Yes	30	21.0	20.0	27	19.3	18.0	8	5.6	5.3	7	5.1	4.7	5	3.4	3
No ⊙	113	79.0	75.3	113	80.7	75.3	135	94.4	90.0	131	94.9	87.3	140	96.6	93
Total Known	143		95.3	140		93.3	143		95.3	138		92.0	145		96
Unknown	7		4.7	10		6.7	7		4.7	12		8.0	5		3
Total	150			150			150			150			150		

⊙ Includes those with no reported military service.

\# Includes fathers of additional and questionable Down's cases and fathers of additional control

SPECIAL SITES AND/OR EQUIPMENT IN MILITARY SERVICE (FROM INTERVIEW)

Ever stationed at radar park?						Ever stationed at missile site?						Did military units use mobile radar?					
Down's			Controls			Down's			Controls			Down's			Controls		
No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total
8	6.6	6.3	7	5.8	5.5	5	4.0	3.9	1	0.8	0.8	9	7.6	7.0	11	9.4	8.6
114	93.4	89.1	114	94.2	89.1	119	96.0	93.0	122	99.2	95.3	109	92.4	85.2	106	90.6	82.8
122		95.3	121		94.5	124		96.9	123		96.1	118		92.2	117		91.4
6		4.7	7		5.5	4		3.1	5		3.9	10		7.8	11		8.6
128			128			128			128			128			128		
7	4.8	3.2	3	1.9	1.4	0	0	0	0	0	0	9	6.3	4.2	4	2.6	1.9
140	95.2	64.8	157	98.1	72.7	153	100.0	70.8	161	100.0	74.5	133	93.7	61.6	150	97.4	69.4
147		68.1	160		74.1	153		70.8	161		74.5	142		65.7	154		71.3
69		31.9	56		25.9	63		29.2	55		25.5	74		34.3	62		28.7
216			216			216			216			216			216		
15	5.6	4.4	10	3.6	2.9	5	1.8	1.4	1	0.4	0.3	18	6.9	5.2	15	5.5	4.4
254	94.4	73.8	271	96.4	78.8	272	98.2	79.1	283	99.6	82.3	242	93.1	70.4	256	94.5	74.4
269		78.2	281		81.7	277		80.5	284		82.6	260		75.6	271		78.8
75		21.8	63		18.3	67		19.5	60		17.4	84		24.4	73		21.2
344			344			344			344			344			344		
8	5.6	5.3	7	5.1	4.7	5	3.4	3.3	2	1.4	1.3	11	8.0	7.3	11	8.3	7.3
135	94.4	90.0	131	94.9	87.3	140	96.6	93.3	138	98.6	92.0	127	92.0	84.7	121	91.7	80.7
143		95.3	138		92.0	145		96.7	140		93.3	138		92.0	132		88.0
7		4.7	12		8.0	5		3.3	10		6.7	12		8.0	18		12.0
150			150			150			150			150			150		

wn's cases and fathers of additional controls, as well as matched pairs.

TABLE R-15A

PATERNAL HISTORY OF WORK IN/NEAR RADAR,MICROWAVE, X-RAY (FROM INTERVIEW)

Prior to Conception of Index Child

SERIES	IN MILITARY						OUTSIDE MILITARY											
Time Relative to Index Conception	Near Radar Installation						In/Near Radar Installation						With Radar					
	Cases			Controls			Cases			Controls			Cases			Controls		
	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total
MATCHED PAIRS																		
CURRENT SERIES																		
Prior	13	10.3	10.2	10	8.0	7.8	2	1.6	1.6	4	3.3	3.1	2	1.6	1.6	8	6.4	6.3
All Other Times	0	0	0	0	0	0	0	0	0	1	0.8	0.8	1	0.8	0.8	0	0	0
None ⊙	113	89.7	88.3	115	92.0	89.8	125	98.4	97.7	118	95.9	92.2	122	97.6	95.3	117	93.6	91.4
Total Known	126		98.4	125		97.7	127		99.2	123		96.1	125		97.7	125		97.7
Unknown	2		1.6	3		2.3	1		0.8	5		3.9	3		2.3	3		2.3
Total	128			128			128			128			128			128		
ORIGINAL SERIES																		
Prior	11	5.6	5.1	6	2.8	2.8	0	0	0	0	0	0	5	2.4	2.3	5	2.3	2.3
All Other Times	0	0	0	0	0	0	0	0	0	0	0	0	3	1.5	1.4	1	0.5	0.5
None ⊙	187	94.4	86.6	205	97.2	94.9	205	100.0	94.9	212	100.0	98.2	199	96.1	92.1	207	97.2	95.8
Total Known	198		91.7	211		97.7	205		94.9	212		98.2	207		95.8	213		98.6
Unknown	18		8.3	5		2.3	11		5.1	4		1.8	9		4.2	3		1.4
Total	216			216			216			216			216			216		
COMBINED SERIES																		
Prior	24	7.4	7.0	16	4.8	4.7	2	0.6	0.6	4	1.2	1.2	7	2.1	2.0	13	3.8	3.8
All Other Times	0	0	0	0	0	0	0	0	0	1	0.3	0.3	4	1.2	1.2	1	0.3	0.3
None ⊙	300	92.6	87.2	320	95.2	93.0	330	99.4	95.9	330	98.5	95.9	321	96.7	93.3	324	95.9	94.2
Total Known	324		94.2	336		97.7	332		96.5	335		97.4	332		96.5	338		98.3
Unknown	20		5.8	8		2.3	12		3.5	9		2.6	12		3.5	6		1.7
Total	344			344			344			344			344			344		
POOLED FATHERS (#)																		
CURRENT SERIES																		
Prior	14	9.5	9.3	11	7.7	7.3	2	1.4	1.3	4	2.9	2.7	2	1.4	1.3	8	5.6	5.3
All Other Times	0	0	0	0	0	0	0	0	0	1	0.7	0.7	1	0.7	0.7	0	0	0
None ⊙	133	90.5	88.7	131	92.3	87.3	146	98.6	97.3	135	96.4	90.0	143	97.9	95.3	134	94.4	89.3
Total Known	147		98.0	142		94.7	148		98.7	140		93.3	146		97.3	142		94.7
Unknown	3		2.0	8		5.3	2		1.3	10		6.7	4		2.7	8		5.3
Total	150			150			150			150			150			150		

⊙ Includes those with no reported military service.

(#) Includes fathers of additional and questionable Down's cases and fathers of additional controls, as well as matched pairs.

TABLE R-15B

PATERNAL HISTORY OF WORK IN/NEAR RADAR, MICROWAVE, X-RAY (FROM INTERVIEW)

Prior to Conception of Index Child

SERIES Time Relative to Index Conception	IN and/or OUT OF MILITARY																	
	Near/Around Radar						With/Near X-ray						With/Near Other Radiation					
	Cases			Controls			Cases			Controls			Cases			Controls		
	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total	No.	% Known	% Total
MATCHED PAIRS																		
CURRENT SERIES																		
Prior	7	5.6	5.5	5	4.0	3.9	7	5.6	5.5	6	4.8	4.7	6	4.8	4.7	3	2.4	2.3
Other Times Only	1	0.8	0.8	0	0	0	2	1.6	1.6	1	0.8	0.8	0	0	0	2	1.6	1.6
None ⊙	118	93.6	92.2	120	96.0	93.8	115	92.7	89.8	118	94.4	92.2	118	95.2	92.2	120	96.0	93.8
Total Known	126		98.4	125		97.7	124		96.9	125		97.7	124		96.9	125		97.7
Unknown	2		1.6	3		2.3	4		3.1	3		2.3	4		3.1	3		2.3
Total	128			128			128			128			128			128		
ORIGINAL SERIES																		
Prior	8	3.9	3.7	6	2.8	2.8	6	2.9	2.8	7	3.3	3.2	2	1.0	0.9	2	0.9	0.9
Other Times Only	3	1.4	1.4	3	1.4	1.4	6	2.9	2.8	4	1.9	1.9	1	0.5	0.5	2	0.9	0.9
None ⊙	196	94.7	90.7	203	95.8	94.0	194	94.2	89.8	202	94.8	93.5	204	98.6	94.4	210	98.1	97.2
Total Known	207		95.8	212		98.1	206		95.4	213		98.6	207		95.8	214		99.1
Unknown	9		4.2	4		1.9	10		4.6	3		1.4	9		4.2	2		0.9
Total	216			216			216			216			216			216		
COMBINED SERIES																		
Prior	15	4.5	4.4	11	3.3	3.2	13	3.9	3.8	13	3.8	3.8	8	2.4	2.3	5	1.5	1.5
Other Times Only	4	1.2	1.2	3	0.9	0.9	8	2.4	2.3	5	1.5	1.5	1	0.3	0.3	4	1.2	1.2
None ⊙	314	94.3	91.3	323	95.8	94.0	309	93.6	89.8	320	94.7	93.0	322	97.3	93.6	330	97.3	95.9
Total Known	333		96.8	337		98.0	330		95.9	338		98.3	331		96.2	339		98.5
Unknown	11		3.2	7		2.0	14		4.1	6		1.7	13		3.8	5		1.5
Total	344			344			344			344			344			344		
POOLED FATHERS (#)																		
CURRENT SERIES																		
Prior	7	4.8	4.7	5	3.5	3.3	8	5.5	5.3	6	4.2	4.0	6	4.1	4.0	4	2.8	2.7
Other Times Only	1	0.7	0.7	0	0	0	2	1.4	1.3	2	1.4	1.3	0	0	0	2	1.4	1.3
None ⊙	139	94.6	92.7	136	96.5	90.7	135	93.1	90.0	134	94.4	89.3	139	95.9	92.7	136	95.8	90.7
Total Known	147		98.0	141		94.0	145		96.7	142		94.7	145		96.7	142		94.7
Unknown	3		2.0	9		6.0	5		3.3	8		5.3	5		3.3	8		5.3
Total	150			150			150			150			150			150		

⊙ Includes those with no reported military service.

(#) Includes fathers of additional and questionable Down's cases and fathers of additional controls, as well as matched pairs.

TABLE MS-1

HISTORY OF MILITARY SERVICE OF FATHERS (FROM INTERVIEW)
Irrespective of Time Relative to Index Birth

Current, Original, and Combined Series

	Matched Pairs						Pooled(#)					
	Cases			Controls			Cases			Controls		
	No.	% Kn.	% Tot.	No.(·)	% Kn.	% Tot.	No.	% Kn.	% Tot.	No.(·)	% Kn.	% Tot.
CURRENT SERIES												
In Service	93	72.7	72.7	91	71.1	71.1	106	71.1	70.7	105	72.4	70.0
Not in Serv.	35	27.3	27.3	37	28.9	28.9	43	28.9	28.7	40	27.6	26.7
Total Kn.	128		100.0	128		100.0	149		99.3	145		96.7
Unk.Serv.	0		0	0			1		0.7	5		3.3
Total	128			128			150			150		
ORIGINAL SERIES												
In Service	134	63.5	62.0	122	57.0	56.5						
Not in Serv.	77	36.5	35.6	92	43.0	42.6						
Total Kn.	211		97.7	214		99.1						
Unk.Serv.	5		2.3	2		0.9						
Total	216			216								
COMBINED SERIES												
In Service	227	67.0	66.0	213	62.3	61.9						
Not in Serv.	112	33.0	32.6	129	37.7	37.3						
Total Kn.	339		98.5	342		99.4						
Unk.Serv.	5		1.5	2		0.6						
Total	344			344								

(#) Includes fathers of additional and questionable Down's cases and fathers of additional controls, as well as matched pairs.

(·) Includes 1 father who served in a foreign military service.

TABLE MS-2

HISTORY OF MILITARY SERVICE OF FATHERS BY BRANCH OF SERVICE (FROM INT

Matched Pairs

Current Series

Time Relative To Conception Of Index Child	ARMY No.	ARMY % Known	ARMY % in Service	ARMY % in this Branch	NAVY No.	NAVY % Known	NAVY % in Service	NAVY % in this Branch	MARINE CORPS No.	MARINE CORPS % Known	MARINE CORPS % in Service	MARINE CORPS % in this Branch	No.
Prior													
Down's Cases	48	37.5	51.6	96.0	25	19.5	26.9	100.0	5	3.9	5.4	100.0	13
Controls	39	30.5	42.9	97.5	25	19.5	27.5	100.0	9	7.0	9.9	100.0	12
During Year Δ													
Down's Cases	1	0.8	1.1	2.0	0	0	0	0	0	0	0	0	0
Controls	0	0	0	0	0	0	0	0	0	0	0	0	0
Prior + During													
Down's Cases	49	38.3	52.7	98.0	25	19.5	26.9	100.0	5	3.9	5.4	100.0	13
Controls	39	30.5	42.9	97.5	25	19.5	27.5	100.0	9	7.0	9.9	100.0	12
After													
Down's Cases	0	0	0	0	0	0	0	0	0	0	0	0	0
Controls	0	0	0	0	0	0	0	0	0	0	0	0	0
In Service, Period Unknown													
Down's Cases	1	0.8	1.1	2.0	0	0	0	0	0	0	0	0	0
Controls	1	0.8	1.1	2.5	0	0	0	0	0	0	0	0	0
Total Known to be in this Branch													
Down's Cases	50	39.1	53.8	100.0	25	19.5	26.9	100.0	5	3.9	5.4	100.0	13
Controls	40	31.3	44.0	100.0	25	19.5	27.5	100.0	9	7.0	9.9	100.0	12
Not in this Branch													
Down's Cases	43	33.6	46.2		68	53.1	73.1		88	68.8	94.6		80
Controls	51	39.8	56.0		66	51.6	72.5		82	64.1	90.1		79
No Milit. Serv.													
Down's Cases	35				35				35				35
Controls	37				37				37				37
Grand Total													
Down's Cases	128				128				128				128
Controls	128				128				128				128

No fathers are of unknown military service status

Δ During year of conception, exact date unknown, either prior to or after conception of index child.

% Known = # in this branch in specified time period / total with known service status, Down's Cases = 128, Controls = 128

% in Service = # in this branch in specified time period / total known to be in any branch of service, Down's Cases 93, Controls = 91

% in this Branch = # in this branch in specified time period / total known to be in this branch of service, e.g. Army: Down's Cases = 50, Controls

...H OF SERVICE (FROM INTERVIEW)

Current Series

	MARINE CORPS		AIR CORPS				COAST GUARD				NATIONAL GUARD			
...n	% in Service	% in this Branch	No.	% Known	% in Service	% in this Branch	No.	% Known	% in Service	% in this Branch	No.	% Known	% in Service	% in this Branch
9	5.4	100.0	13	10.2	14.0	100.0	0	0	0	0	2	1.6	2.2	66.7
0	9.9	100.0	12	9.4	13.2	100.0	2	1.6	2.2	100.0	3	2.3	3.3	100.0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	5.4	100.0	13	10.2	14.0	100.0	0	0	0	0	2	1.6	2.2	66.7
0	9.9	100.0	12	9.4	13.2	100.0	2	1.6	2.2	100.0	3	2.3	3.3	100.0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	1	0.8	1.1	3.3
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	5.4	100.0	13	10.2	14.0	100.0	0	0	0	0	3	2.3	3.3	100.0
0	9.9	100.0	12	9.4	13.2	100.0	2	1.6	2.2	100.0	3	2.3	3.3	100.0
	94.6		80	62.5	86.2		93	72.7	100.0		90	70.3	96.8	
	90.1		79	61.7	86.8		89	69.5	97.8		88	68.8	96.7	
			35				35				35			
			37				37				37			
			128				128				128			
			128				128				128			

...tary service status

... of index child.

= 128

...ols = 91

... Cases = 50, Controls = 40; Navy: Down's Cases = 25, Controls = 25, etc.

TABLE MS-3

HISTORY OF MILITARY SERVICE OF FATHERS BY BRANCH OF SERVICE (FROM INTERVI

Matched Pairs

Original Series

Time Relative To Conception Of Index Child	ARMY				NAVY				MARINE CORPS			
	No.	% Known ⊙	% in Service ⊗	% in this Branch ⊛	No.	% Known	% in Service	% in this Branch	No.	% Known	% in Service	% in this Branch
Prior												
Down's Cases	68	32.2	50.7	95.8	37	17.5	27.6	100.0	8	3.8	6.0	100.0
Controls	60	28.0	49.2	100.0	36	16.8	29.5	100.0	3	1.4	2.5	100.0
During Year Δ												
Down's Cases	0	0	0	0	0	0	0	0	0	0	0	0
Controls	0	0	0	0	0	0	0	0	0	0	0	0
Prior + During												
Down's Cases	68	32.2	50.7	95.8	37	17.5	27.6	100.0	8	3.8	6.0	100.0
Controls	60	28.0	0	100.0	36	16.8	29.5	100.0	3	1.4	2.5	100.0
After												
Down's Cases	3	1.4	2.2	4.2	0	0	0	0	0	0	0	0
Controls	0	0	0	0	0	0	0	0	0	0	0	0
In Service, Period Unknown												
Down's Cases	0	0	0	0	0	0	0	0	0	0	0	0
Controls	0	0	0	0	0	0	0	0	0	0	0	0
Total Known to be in this Branch												
Down's Cases	71	33.6	53.0	100.0	37	17.5	27.6	100.0	8	3.8	6.0	100.0
Controls	60	28.0	49.2	100.0	36	16.8	29.5	100.0	3	1.4	2.5	100.0
Not in this Branch												
Down's Cases	63	29.9	47.0		97	46.0	72.4		126	59.7	94.0	
Controls	62	29.0	50.8		86	40.2	70.5		119	55.6	97.5	
No Milit.Serv.												
Down's Cases	77				77				77			
Controls	92				92				92			
Grand Total												
Down's Cases	216				216				216			
Controls	216				216				216			

5 case fathers and 2 control fathers are of

Δ During year of conception, exact date unknown, either prior to or after conception of inde

⊙ % Known = $\frac{\text{\# in this branch in specified time period}}{\text{total with known service status}}$; (5 case fathers & 2 control fathers a

⊗ % in Service = $\frac{\text{\# in this branch in specified time period}}{\text{total known to be in any branch of service}}$, Down's Cases = 134, Controls =

⊛ % in this Branch = $\frac{\text{\# in this branch in specified time period}}{\text{total known to be in this branch of service}}$, e.g., Army: Down's Cases

SERVICE (FROM INTERVIEW)

iginal Series

MARINE CORPS			AIR CORPS				COAST GUARD				NATIONAL GUARD			
% nown	% in Service	% in this Branch	No.	% Known	% in Service	% in this Branch	No.	% Known	% in Service	% in this Branch	No.	% Known	% in Service	% in this Branch
3.8	6.0	100.0	19	9.0	14.2	100.0	1	0.5	0.8	100.0	0	0	0	0
1.4	2.5	100.0	18	8.4	14.8	100.0	5	2.3	4.1	100.0	1	0.5	0.8	100.0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3.8	6.0	100.0	19	9.0	14.2	100.0	1	0.5	0.8	100.0	0	0	0	0
1.4	2.5	100.0	18	8.4	14.8	100.0	5	2.3	4.1	100.0	1	0.5	0.8	100.0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	1	0.5	0.7	100.0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3.8	6.0	100.0	19	9.0	14.2	100.0	1	0.5	0.8	100.0	1	0.5	0.7	100.0
1.4	2.5	100.0	18	8.4	14.8	100.0	5	2.3	4.1	100.0	1	0.5	0.8	100.0
59.7	94.0		115	54.5	85.8		133	63.0	99.3		133	63.0	99 3	
55.6	97.5		104	48.6	85.2		117	54.7	95.9		121	56.5	99.2	
			77				77				77			
			92				92				92			
			216				216				216			
			216				216				216			

control fathers are of unknown military status

ter conception of index child.

& 2 control fathers are of unknown military status), Down's Cases = 211, Controls = 214

ses = 134, Controls = 122

., Army: Down's Cases = 71, Controls = 60; Navy: Down's Cases = 37, Controls = 36 etc.

TABLE MS-4

HISTORY OF MILITARY SERVICE OF FATHERS BY BRANCH OF S

Matched Pairs

Current & Orig

Time Relative to Concept. of Index Child	ARMY No.	ARMY % Known ⊙	ARMY % in Service ⊗	ARMY % in this Branch ⊛	NAVY No.	NAVY % Known	NAVY % in Service	NAVY % in this Branch	MARINE CORPS No.	MARINE CORPS % Known	MARINE CORPS % in Service	MARINE CORPS % in this Branch	AIR No.	AIR % Known	Se
Prior															
Down's Cases	116	34.2	51.1	95.9	62	18.3	27.3	100.0	13	3.8	5.7	100.0	32	9.4	
Controls	99	29.0	46.5	99.0	61	17.8	28.6	100.0	12	3.5	5.6	100.0	30	8.8	
During Yr. △															
Down's Cases	1	0.3	0.4	0.8	0	0	0	0	0	0	0	0	0	0	
Controls	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Prior & During															
Down's Cases	117	34.5	51.5	96.7	62	18.3	27.3	100.0	13	3.8	5.7	100.0	32	9.4	
Controls	99	29.0	46.5	99.0	61	17.8	28.6	100.0	12	3.5	5.6	100.0	30	8.8	
After															
Down's Cases	3	0.9	1.3	2.5	0	0	0	0	0	0	0	0	0	0	
Controls	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
In Service, Period Unknown															
Down's Cases	1	0.3	0.4	0.8	0	0	0	0	0	0	0	0	0	0	
Controls	1	0.3	0.5	1.0	0	0	0	0	0	0	0	0	0	0	
Total Known in this Branch															
Down's Cases	121	35.7	53.3	100.0	62	18.3	27.3	100.0	13	3.8	5.7	100.0	32	9.4	
Controls	100	29.2	46.9	100.0	61	17.8	28.6	100.0	12	3.5	5.6	100.0	30	8.8	
Not in this Br.															
Down's Cases	106	31.3	46.7		165	48.7	72.7		214	63.1	94.3		195	57.5	
Controls	113	33.0	53.1		152	44.4	71.4		201	58.8	94.4		183	53.5	
Unknown Serv. Status															
Down's Cases	5				5				5				5		
Controls	2				2				2				2		
No Milit.Serv.															
Down's Cases	112				112				112				112		
Controls	129				129				129				129		
Grand Total															
Down's Cases	344				344				344				344		
Controls	344				344				344				344		

△ During year of conception, exact date unknown, either prior to or after concepti

⊙ % Known = # in this branch in specified time period / total with known service status, Down's Cases = 339,

⊗ % in Service = # in this branch in specified time period / total known to be in any branch of service, Down's Cases =

⊛ % in this Branch = # in this branch in specified time period / Total known to be in this branch of service, e.g. Army: Dow

ARY SERVICE OF FATHERS BY BRANCH OF SERVICE (FROM INTERVIEW)

ched Pairs Current & Original Series Combined

MARINE CORPS				AIR CORPS				COAST GUARD				NATIONAL GUARD			
No.	% Known	% in Service	% in this Branch	No.	% Known	% in Service	% in this Branch	No.	% Known	% in Service	% in this Branch	No.	% Known	% in Service	% in this Branch
13	3.8	5.7	100.0	32	9.4	14.1	100.0	1	0.3	0.4	100.0	2	0.6	0.9	50.0
12	3.5	5.6	100.0	30	8.8	14.1	100.0	7	2.0	3.3	100.0	4	1.2	1.9	100.0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13	3.8	5.7	100.0	32	9.4	14.1	100.0	1	0.3	0.4	100.0	2	0.6	0.9	50.0
12	3.5	5.6	100.0	30	8.8	14.1	100.0	7	2.0	3.3	100.0	4	1.2	1.9	100.0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	2	0.6	0.9	50.0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13	3.8	5.7	100.0	32	9.4	14.1	100.0	1	0.3	0.4	100.0	4	1.2	1.8	100.0
12	3.5	5.6	100.0	30	8.8	14.1	100.0	7	2.0	3.3	100.0	4	1.2	1.9	100.0
214	63.1	94.3		195	57.5	85.9		226	66.7	99.6		223	65.8	98.2	
201	58.8	94.4		183	53.5	85.9		206	60.2	96.7		209	61.1	98.1	
5				5				5				5			
2				2				2				2			
112				112				112				112			
129				129				129				129			
344				344				344				344			
344				344				344				344			

wn, either prior to or after conception of index child

ime period

us , Down's Cases = 339, Controls = 342

ied time period

branch of service, Down's Cases = 227, Controls = 213

cified time period

is branch of service, e.g. Army: Down's Cases = 121, Controls = 100; Navy: Down's Cases = 62, Controls= 61, etc.

TABLE MS-5

RECORD OF MILITARY SERVICE OF FATHERS FROM NAS COMPARED TO INTERVIEW IRRESPECTIVE OF TIME RELATIVE TO INDEX BIRTH

Current, Original, and Combined Series

	CURRENT SERIES				ORIGINAL SERIES				COMBINED SERIES			
	Down's Cases		Controls		Down's Cases		Controls		Down's Cases		Controls	
Matched Pairs	No.	%Tot.	No.	%Tot.	No.	%Tot.		%Tot.	No.	%Tot.	No.	%Tot.
No Record from NAS & No Service Reported on Interview	36	28.1	38	29.7	77	35.6	92	42.6	113	32.9	130	37.8
No Record from NAS, but Service Reported on Interview	6	4.7	7	5.5	10	4.6	14	6.5	16	4.7	21	6.1
No Record from NAS	42	32.8	45	35.2	87	40.2	106	49.1	129	37.5	151	43.9
Service Verified by NAS	82	64.1	81	63.3	128	59.3	107	49.5	210	61.1	188	54.7
Service Verified by NAS, but Report Incomplete	4	3.1	2	1.6	1	0.5	3	1.4	5	1.5	5	1.5
Total Service Verification by NAS	86	67.2	83	64.8	129	59.7	110	50.9	215	62.5	193	56.1
Total Fathers	128	100.0	128	100.0	216	100.0	216	100.0	344	100.0	344	100.0
Pooled Groups (#)												
No Record from NAS & No Service Reported on Interview	44	29.3	41	27.3								
No Record from NAS, but Service Reported on Interview	8	5.3	13	8.7								
No Record from NAS	52	34.6	54	36.0								
Service Verified by NAS	94	62.7	93	62.0								
Service Verified by NAS, but Report Incomplete	4	2.7	3	2.0								
Total Service Verification by NAS	98	65.3	96	64.0								
Total Fathers	150	100.0	150	100.0								

(#) Includes fathers of additional & questionable Down's cases and fathers of additional controls, as well as matched pairs.

TABLE MS-6

HISTORY OF MILITARY SERVICE OF FATHERS BY BRANCH (

Matched Pairs Currer

Time Relative to Conception of Index Child	ARMY No.	ARMY % Known in this Branch	ARMY % Total	NAVY No.	NAVY % Known in this Branch	NAVY % Total	MARINE CORPS No.	MARINE CORPS % Known in this Branch	MARINE CORPS % Total	AIR CORPS No.	AIR CORPS % Known in this Branch	AIR CORPS % Total
Prior												
Down's Cases	48	100.0	37.5	25	100.0	19.5	4	100.0	3.1	7	100.0	5.5
Controls	44	100.0	34.4	20	100.0	15.6	8	100.0	6.3	6	100.0	4.7
During Yr.												
Down's Cases	0	0	0	0	0	0	0	0	0	0	0	0
Controls	0	0	0	0	0	0	0	0	0	0	0	0
Prior & During												
Down's Cases	48	100.0	37.5	25	100.0	19.5	4	100.0	3.1	7	100.0	5.5
Controls	44	100.0	34.4	20	100.0	15.6	8	100.0	6.3	6	100.0	4.7
After												
Down's Cases	0	0	0	0	0	0	0	0	0	0	0	0
Controls	0	0	0	0	0	0	0	0	0	0	0	0
In Service, Period Unknown												
Down's Cases	0	0	0	0	0	0	0	0	0	0	0	0
Controls	0	0	0	0	0	0	0	0	0	0	0	0
Tot. Known in this Branch												
Down's Cases	48	100.0	37.5	25	100.0	19.5	4	100.0	3.1	7	100.0	5.5
Controls	44	100.0	34.4	20	100.0	15.6	8	100.0	6.3	6	100.0	4.7
No Record of Service, This Branch												
Down's Cases	80		62.5	103		80.5	124		96.9	121		94.5
Controls	84		65.6	108		84.4	120		93.8	122		95.3
Total												
Down's Cases	128		100.0	128		100.0	128		100.0	128		100.0
Controls	128		100.0	128		100.0	128		100.0	128		100.0

During year of conception, exact date unknown, either prior to or after conception of index

Calculated using as the denominator the number of fathers whose service in a particular bra

HISTORY OF MILITARY SERVICE OF FATHERS BY BRANCH OF SERVICE (FROM NAS)

Matched Pairs

Current Series

NAVY		MARINE CORPS			AIR CORPS			COAST GUARD			NATIONAL GUARD		
Known n this ranch	% Total	No.	% Known in this Branch	% Total	No.	% Known in this Branch	% Total	No.	% Known in this Branch	% Total	No.	% Known in this Branch	% Total
100.0	19.5	4	100.0	3.1	7	100.0	5.5	0	0	0	2	100.0	1.6
100.0	15.6	8	100.0	6.3	6	100.0	4.7	2	100.0	1.6	2	100.0	1.6
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0
100.0	19.5	4	100.0	3.1	7	100.0	5.5	0	0	0	2	100.0	1.6
100.0	15.6	8	100.0	6.3	6	100.0	4.7	2	100.0	1.6	2	100.0	1.6
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0
100.0	19.5	4	100.0	3.1	7	100.0	5.5	0	0	0	2	100.0	1.6
100.0	15.6	8	100.0	6.3	6	100.0	4.7	2	100.0	1.6	2	100.0	1.6
	80.5	124		96.9	121		94.5	128		100.0	126		98.4
	84.4	120		93.8	122		95.3	126		98.4	126		98.4
	100.0	128		100.0	128		100.0	128		100.0	128		100.0
	100.0	128		100.0	128		100.0	128		100.0	128		100.0

nknown, either prior to or after conception of index child.

number of fathers whose service in a particular branch of the military was verified by NAS.

TABLE MS-7

HISTORY OF MILITARY SERVICE OF FATHERS BY BRANCH OF SERVICE
Matched Pairs Original Series

Time Relative to Conception of Index Child	ARMY			NAVY			MARINE CORPS			AIR CORPS			
	No.	% Known in this Branch ⊙	% Total	No.	% Known in this Branch	% Total	No.	% Known in this Branch	% Total	No.	% Known in this Branch	% Total	No.
Prior													
Down's Cases	80	97.6	37.0	35	100.0	16.2	8	100.0	3.7	4	100.0	1.9	1
Controls	63	98.4	29.2	31	100.0	14.4	2	100.0	0.9	7	100.0	3.2	4
During Yr. ⊗													
Down's Cases	0	0	0	0	0	0	0	0	0	0	0	0	0
Controls	0	0	0	0	0	0	0	0	0	0	0	0	0
Prior & During													
Down's Cases	80	97.6	37.0	35	100.0	16.2	8	100.0	3.7	4	100.0	1.9	1
Controls	63	98.4	29.2	31	100.0	14.4	2	100.0	0.9	7	100.0	3.2	4
After													
Down's Cases	1	1.2	0.5	0	0	0	0	0	0	0	0	0	0
Controls	1	1.6	0.5	0	0	0	0	0	0	0	0	0	0
In Service, Period Unknown													
Down's Cases	1	1.2	0.5	0	0	0	0	0	0	0	0	0	0
Controls	0	0	0	0	0	0	0	0	0	0	0	0	0
Total Known in this Branch													
Down's Cases	82	100.0	38.0	35	100.0	16.2	8	100.0	3.7	4	100.0	1.9	1
Controls	64	100.0	29.6	31	100.0	14.4	2	100.0	0.9	7	100.0	3.2	4
No Record of Service, This Branch													
Down's Cases	134		62.1	181		83.8	208		96.3	212		98.2	215
Controls	152		70.4	185		85.7	214		99.1	209		96.8	212
Total													
Down's Cases	216		100.0	216		100.0	216		100.0	216		100.0	216
Controls	216		100.0	216		100.0	216		100.0	216		100.0	216

⊗ During year of conception, exact date unknown, either prior to or after conception of index chil

⊙ Calculated using as the denominator the number of fathers whose service in a particular branch o

Y OF MILITARY SERVICE OF FATHERS BY BRANCH OF SERVICE (FROM NAS)
Matched Pairs Original Series

VY		MARINE CORPS			AIR CORPS			COAST GUARD			NATIONAL GUARD		
own this ch	% Total	No.	% Known in this Branch	% Total	No.	% Known in this Branch	% Total	No.	% Known in this Branch	% Total	No.	% Known in this Branch	% Total
0.0	16.2	8	100.0	3.7	4	100.0	1.9	1	100.0	0.5	0	0	0
0.0	14.4	2	100.0	0.9	7	100.0	3.2	4	100.0	1.9	1	100.0	0.5
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.0	16.2	8	100.0	3.7	4	100.0	1.9	1	100.0	0.5	0	0	0
0.0	14.4	2	100.0	0.9	7	100.0	3.2	4	100.0	1.9	1	100.0	0.5
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.0	16.2	8	100.0	3.7	4	100.0	1.9	1	100.0	0.5	0	0	0
0.0	14.4	2	100.0	0.9	7	100.0	3.2	4	100.0	1.9	1	100.0	0.5
	83.8	208		96.3	212		98.2	215		99.5	216		100.0
	85.7	214		99.1	209		96.8	212		98.2	215		99.5
	100.0	216		100.0	216		100.0	216		100.0	216		100.0
	100.0	216		100.0	216		100.0	216		100.0	216		100.0

nown, either prior to or after conception of index child.
umber of fathers whose service in a particular branch of the military was verified by NAS.

TABLE MS-8

HISTORY OF MILITARY SERVICE OF FATHERS BY BRANCH OF SERVIC
Matched Pairs Current & Original Series Combi

Time Relative to Birth of Index Child	ARMY No.	ARMY % Known in this Branch	ARMY % Total	NAVY No.	NAVY % Known in this Branch	NAVY % Total	MARINE CORPS No.	MARINE CORPS % Known in this Branch	MARINE CORPS % Total	AIR CORPS No.	AIR CORPS % Known in this Branch	AIR CORPS % Total	No
Prior													
Down's Cases	128	98.5	37.2	60	100.0	17.4	12	100.0	3.5	11	100.0	3.2	1
Controls	107	99.1	31.1	51	100.0	14.8	10	100.0	2.9	13	100.0	3.8	6
During Yr.													
Down's Cases	0	0	0	0	0	0	0	0	0	0	0	0	0
Controls	0	0	0	0	0	0	0	0	0	0	0	0	0
Prior & During													
Down's Cases	128	98.5	37.2	60	100.0	17.4	12	100	3.5	11	100.0	3.2	1
Controls	107	99.1	31.1	51	100.0	14.8	10	100.	2.9	13	100.0	3.8	6
After													
Down's Cases	1	0.8	0.3	0	0	0	0	0	0	0	0	0	0
Controls	1	0.9	0.3	0	0	0	0	0	0	0	0	0	0
In Service, Period Unknown													
Down's Cases	1	0.8	0.3	0	0	0	0	0	0	0	0	0	0
Controls	0	0	0	0	0	0	0	0	0	0	0	0	0
Total Known in this Branch													
Down's Cases	130	100.0	37.8	60	100.0	17.4	12	100.0	3.5	11	100.0	3.2	1
Controls	108	100.0	31.4	51	100.0	14.8	10	100.0	2.9	13	100.0	3.8	6
No Record of Service, This Branch													
Down's Cases	214		62.2	284		82.6	332		96.5	333		96.8	343
Controls	236		68.6	293		85.2	334		97.1	331		96.2	338
Total													
Down's Cases	344		100.0	344		100.0	344		100.0	344		100.0	344
Controls	344		100.0	344		100.0	344		100.0	344		100.0	344

(x) During year of conception, exact date unknown, either prior to or after conception of index chil

(o) Calculated using as the denominator the number of fathers whose service in a particular branch c

Y OF MILITARY SERVICE OF FATHERS BY BRANCH OF SERVICE (FROM NAS)
Matched Pairs Current & Original Series Combined

Y		MARINE CORPS			AIR CORPS			COAST GUARD			NATIONAL GUARD		
wn is h	% Total	No.	% Known in this Branch	% Total	No.	% Known in this Branch	% Total	No.	% Known in this Branch	% Total	No.	% Known in this Branch	% Total
.0	17.4	12	100.0	3.5	11	100.0	3.2	1	100.0	0.3	2	100.0	0.6
.0	14.8	10	100.0	2.9	13	100.0	3.8	6	100.0	1.7	3	100.0	0.9
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0
.0	17.4	12	100.0	3.5	11	100.0	3.2	1	100.0	0.3	2	100.0	0.6
.0	14.8	10	100.0	2.9	13	100.0	3.8	6	100.0	1.7	3	100.0	0.9
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0
.0	17.4	12	100.0	3.5	11	100.0	3.2	1	100.0	0.3	2	100.0	0.6
.0	14.8	10	100.0	2.9	13	100.0	3.8	6	100.0	1.7	3	100.0	0.9
	82.6	332		96.5	333		96.8	343		99.7	342		99.4
	85.2	334		97.1	331		96.2	338		98.3	341		99.1
	100.0	344		100.0	344		100.0	344		100.0	344		100.0
	100.0	344		100.0	344		100.0	344		100.0	344		100.0

own, either prior to or after conception of index child.
mber of fathers whose service in a particular branch of the military was verified by NAS.

TABLE MS-9

SUMMARY OF HISTORY OF MILITARY SERVICE OF

Matched Pairs - Current, Original

Time Relative to Conception of Index Child	ARMY				NAVY				MARINE CORPS				AIR CORPS		
	Interview		NAS		Interview		NAS		Interview		NAS		Interview		
	No.	% Tot.	No.	% Tot.	No.	% Tot.	No.	% Tot.	No.	% Tot.	No.	% Tot.	No.	% Tot.	No.
CURRENT SERIES															
Prior +															
Downs Cases	49‡	38.3	48	37.5	25	19.5	25	19.5	5	3.9	4	3.1	13	10.2	7
Controls	39	30.5	44	34.4	25	19.5	20	15.6	9	7.0	8	6.3	12	9.4	6
Other Times Only															
Down's Cases	1	0.8	0	0	0	0	0	0	0	0	0	0	0	0	0
Controls	1	0.8	0	0	0	0	0	0	0	0	0	0	0	0	0
Unknown															
Down's Cases	0	0	42□	32.8	0	0	42□	32.8	0	0	42□	32.8	0	0	42□
Controls	0	0	46□	35.9	0	0	46□	35.9	0	0	46□	35.9	0	0	46□
Total															
Down's Cases	128		128		128		128		128		128		128		128
Controls	128		128		128		128		128		128		128		128
ORIGINAL SERIES															
Prior +															
Down's Cases	68	31.5	80	37.0	37	17.1	35	16.2	8	3.7	8	3.7	19	8.8	4
Controls	60	27.8	63	29.2	36	16.7	31	14.4	3	1.4	2	0.9	18	8.3	7
Other Times Only															
Down's Cases	3	1.4	2	0.9	0	0	0	0	0	0	0	0	0	0	0
Controls	0	0	1	0.4	0	0	0	0	0	0	0	0	0	0	0
Unknown															
Down's Cases	5	2.3	86□	39.8	5	2.3	86□	39.8	5	2.3	86□	39.8	5	2.3	86□
Controls	2	0.9	107□	49.5	2	0.9	107□	49.5	2	0.9	107□	49.5	2	0.9	107□
Total															
Down's Cases	216		216		216		216		216		216		216		216
Controls	216		216		216		216		216		216		216		216
COMBINED SERIES															
Prior +															
Down's Cases	117‡	34.0	128	37.2	62	18.0	60	17.4	13	3.8	12	3.5	32	9.3	11
Controls	99	28.8	107	31.1	61	17.7	51	14.8	12	3.5	10	2.9	30	8.7	13
Other Times Only															
Down's Cases	4	1.2	2	0.6	0	0	0	0	0	0	0	0	0	0	0
Controls	1	0.3	1	0.3	0	0	0	0	0	0	0	0	0	0	0
Unknown															
Down's Cases	5	1.5	128□	37.2	5	1.5	128□	37.2	5	1.5	128□	37.2	5	1.5	128□
Controls	2	0.6	153□	44.5	2	0.6	153□	44.5	2	0.6	153□	44.5	2	0.6	153□
Total															
Down's Cases	344		344		344		344		344		344		344		344
Controls	344		344		344		344		344		344		344		344

+ Including all fathers who served in the military prior to conception of index child and who may also have

‡ Including 1 father indicating service during year of conception, exact date unknown, may have been prior

□ "Unknown" here = no record of military service from NAS, and includes, therefore, fathers with no militar

⊗ Not including 1 father who served in a foreign military service

TARY SERVICE OF FATHERS (FROM INTERVIEW AND NAS)
rrent, Original and Combined Series

AIR CORPS				COAST GUARD				NATIONAL GUARD				ANY BRANCH OF SERVICE			
nterview		NAS		Interview		NAS		Interview		NAS		Interview		NAS	
o.	% Tot.	No.	% Tot.	No.	% Tot.	No.	% Tot.	No.	% Tot.	No.	% Tot.	No.	% Tot.	No.	% Tot.
13	10.2	7	5.5	0	0	0	0	2	1.6	2	1.6	91	71.1	84	65.6
12	9.4	6	4.7	2	1.6	2	1.6	3	2.3	2	1.6	89	69.5	81	63.3
0	0	0	0	0	0	0	0	1	0.8	0	0	2	1.6	0	0
0	0	0	0	0	0	0	0	0	0	0	0	1	0.8	0	0
0	0	42	32.8	0	0	42	32.8	0	0	42	32.8	0	0	9	7.0
0	0	46	35.9	0	0	46	35.9	0	0	46	35.9	0	0	9	7.0
28		128		128		128		128		128		128	100.0	128	100.0
28		128		128		128		128		128		128	100.0	128	100.0
19	8.8	4	1.8	1	0.4	1	0.4	0	0	0	0	130	60.2	127	58.8
18	8.3	7	3.2	5	2.3	4	1.8	1	0.4	1	0.4	122	56.5	107	49.5
0	0	0	0	0	0	0	0	1	0.4	0	0	4	1.9	2	0.9
0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.5
5	2.3	86	39.8	5	2.3	86	39.8	5	2.3	86	39.8	5	2.3	10	4.6
2	0.9	107	49.5	2	0.9	107	49.5	2	0.9	107	49.5	2	0.9	16	7.4
16		216		216		216		216		216		216	100.0	216	100.0
16		216		216		216		216		216		216	100.0	216	100.0
2	9.3	11	3.2	1	0.3	1	0.3	2	0.6	2	0.6	221	64.2	211	61.3
0	8.7	13	3.8	7	2.0	6	1.7	4	1.2	3	0.9	211	61.3	188	54.6
	0	0	0	0	0	0	0	2	0.6	0	0	6	1.7	2	0.6
	0	0	0	0	0	0	0	0	0	0	0	1	0.3	1	0.3
	1.5	128	37.2	5	1.5	128	37.2	5	1.5	128	37.2	5	1.5	19	5.5
	0.6	153	44.5	2	0.6	153	44.5	2	0.6	153	44.5	2	0.6	25	7.3
		344		344		344		344		344		344	100.0	344	100.0
		344		344		344		344		344		344	100.0	344	100.0

may also have served any other times

ve been prior to conception of index child

ith no military service, as well as fathers of unknown military status

TABLE MED-1A

SUMMARY OF PARENTAL MEDICAL RADIATION EXPOSURE PRIOR TO CONCEPTION OF IND

Current Series

Type of Radiation	Mothers of Down's		Mothers of Controls		Down
MATCHED PAIRS	No.	%	No.	%	No.
No radiation	78	64.5	76	62.8	38
Radiation					
Diagnostic only	23	19.0	23	19.0	63
Fluoroscopic only	7	5.8	9	7.4	0
Therapeutic only	9	7.4	4	3.3	0
Diagnostic and Fluoroscopic	2	1.7	6	5.0	20
Diagnostic and Therapeutic	1	0.8	2	1.7	4
Fluoroscopic and Therapeutic	0	0	0	0	0
Diag., Fluoro., and Therap.	1	0.8	1	0.8	0
Any Fluoroscopic	10	8.3	16	13.2	20
Any Therapeutic	11	9.1	7	5.8	4
Number Known	121	(94.5)	121	(94.5)	125
Number Unknown	7	(5.5)	7	(5.5)	3
Total	128		128		128
POOLED #					
No radiation	92	65.2	93	65.5	43
Radiation					
Diagnostic only	27	19.1	24	16.9	75
Fluoroscopic only	8	5.7	11	7.7	0
Therapeutic only	10	7.1	4	2.8	0
Diagnostic and Fluoroscopic	2	1.4	6	4.2	23
Diagnostic and Therapeutic	1	0.7	2	1.4	4
Fluoroscopic and Therapeutic	0	0	1	0.7	0
Diag., Fluoro., and Therap.	1	0.7	1	0.7	0
Any Fluoroscopic	11	7.8	19	13.4	23
Any Therapeutic	12	8.5	8	5.6	4
Number Known	141	(94.0)	142	(94.7)	145
Number Unknown	9	(6.0)	8	(5.3)	5
Total	150		150		150

% = Percent known
( ) = Percent total
= Includes mothers and fathers of additional and questionable mongols and mothers and fathers as well as matched pairs.

AL MEDICAL RADIATION EXPOSURE PRIOR TO CONCEPTION OF INDEX CHILD

Current Series

Mothers of Down's No.	Mothers of Down's %	Mothers of Controls No.	Mothers of Controls %	Fathers of Down's No.	Fathers of Down's %	Fathers of Controls No.	Fathers of Controls %
78	64.5	76	62.8	38	30.4	35	28.5
23	19.0	23	19.0	63	50.4	61	49.6
7	5.8	9	7.4	0	0	2	1.6
9	7.4	4	3.3	0	0	1	0.8
2	1.7	6	5.0	20	16.0	17	13.8
1	0.8	2	1.7	4	3.2	4	3.2
0	0	0	0	0	0	0	0
1	0.8	1	0.8	0	0	3	2.4
10	8.3	16	13.2	20	16.0	22	17.9
11	9.1	7	5.8	4	3.2	8	6.5
121	(94.5)	121	(94.5)	125	(97.7)	123	(96.1)
7	(5.5)	7	(5.5)	3	(2.3)	5	(3.9)
128		128		128		128	
92	65.2	93	65.5	43	29.7	43	30.7
27	19.1	24	16.9	75	51.7	68	48.6
8	5.7	11	7.7	0	0	2	1.4
10	7.1	4	2.8	0	0	1	0.7
2	1.4	6	4.2	23	15.9	18	12.9
1	0.7	2	1.4	4	2.8	5	3.6
0	0	1	0.7	0	0	0	0
1	0.7	1	0.7	0	0	3	2.1
11	7.8	19	13.4	23	15.9	23	16.4
12	8.5	8	5.6	4	2.8	9	6.4
141	(94.0)	142	(94.7)	145	(96.7)	140	(93.3)
9	(6.0)	8	(5.3)	5	(3.3)	10	(6.7)
150		150		150		150	

dditional and questionable mongols and mothers and fathers of additional controls,

TABLE MED-1B

SUMMARY OF MATERNAL MEDICAL RADIATION EXPOSURE
PRIOR TO CONCEPTION PLUS DURING FIRST MONTH OF PREGNANCY [+]
Current Series

	Matched Pairs				Pooled Groups			
	Mothers of				Mothers of			
	Down's		Controls		Down's		Controls	
	#	%	#	%	#	%	#	%
Type of Radiation								
No radiation	43	34.4	42	33.6	50	34.2	53	36.3
Radiation								
Diagnostic only	61	48.8	59	47.2	73	50.0	65	44.5
Fluoroscopic only	2	1.6	3	2.4	3	2.1	3	2.1
Therapeutic only	7	5.6	1	0.8	8	5.5	1	0.7
Diagnostic and Fluoroscopic	8	6.4	13	10.4	8	5.5	15	10.3
Diagnostic and Therapeutic	3	2.4	5	4.0	3	2.1	6	4.1
Fluoroscopic and Therapeutic	-	-	-	-	-	-	-	-
Diagnostic, Fluoroscopic, and Therapeutic	1	0.8	2	1.6	1	0.7	3	2.1
Number Known	125	97.7	125	97.7	146	97.3	146	97.3
Number Unknown	3	2.3	3	2.3	4	2.7	4	2.7
Total	128		128		150		150	

+ Also includes exact date unknown that year.

TABLE MED-2A

PARENTAL DIAGNOSTIC X-RAY EXPOSURE:
SITE OF EXPOSURE PRIOR TO CONCEPTION OF INDEX CHILD

Current Series

Type ⊙ of diagnostic x-ray	Mothers of:				Fathers of:			
	Cases		Controls		Cases		Controls	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent
MATCHED PAIRS								
Chest x-ray	43	33.6	45	35.2	54	42.2	49	38.3
Gallbladder series	6	4.7	11	8.6	2	1.6	3	2.3
Kidney, including IVP	7	5.5	8	6.2	4	3.1	10	7.8
Sto-Int-Abd	9	7.0	13	10.2	24	18.8	25	19.5
Other organs	29	22.7	31	24.2	52	40.6	61	47.7
Total	128		128		128		128	
POOLED (#)								
Chest x-ray	50	33.3	49	32.7	60	40.0	52	34.7
Gallbladder series	6	4.0	12	8.0	6	4.0	3	2.0
Kidney, including IVP	7	4.7	9	6.0	7	4.7	10	6.7
Sto-Int-Abd	9	6.0	15	10.0	32	21.3	28	18.7
Other organs	33	22.0	34	22.7	62	41.3	67	44.7
Total	150		150		150		150	

(#) Includes mothers and fathers of additional and questionable mongols and mothers and fathers of additional controls, as well as matched pairs.

⊙ Types of diagnostic x-ray listed are not mutually exclusive.

TABLE MED.2B

PARENTAL DIAGNOSTIC X-RAY EXPOSURES: SITE OF EXPOSURE[x]

Current Series

Type of diagnostic x-ray	Mothers of:				Fathers of:			
	Cases		Controls		Cases		Controls	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent
MATCHED FAIRS								
Chest x-ray	48	37.5	51	39.8	55	43.0	52	40.6
Gallbladder series	6	4.7	14	10.9	2	1.6	3	2.3
Kidney, including IVP	9	7.0	9	7.0	5	3.9	10	7.8
Sto-Int-Abd	11	8.6	16	12.5	24	18.8	26	20.3
Other organs	32	25.0	35	27.3	61	47.7	62	48.4
Total	128		128		128		128	
POOLED#								
Chest x-ray	58	38.7	59	39.3	61	40.7	57	38.0
Gallbladder series	6	4.0	15	10.0	6	4.0	3	2.0
Kidney, including IVP	9	6.0	13	8.7	8	5.3	10	6.7
Sto-Int-Abd	11	7.3	18	12.0	32	21.3	29	19.3
Other organs	36	24.0	39	26.0	71	47.3	69	46.0
Total	150		150		150		150	

[x] Prior to conception of index plus during year of conception, exact date unknown - could have been prior to or after conception of index child.

Includes mothers and fathers of additional and questionable mongols and mothers and fathers of additional controls, as well as matched pairs.

MED-3A

MATERNAL FLUOROSCOPIC EXPOSURE PRIOR TO CONCEPTION OF INDEX CHILD

Current Series

Number of sessions	Down's						Controls					
	Chest		Abdomen		Other		Chest		Abdomen		Other	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Matched Pairs		% Kn.		% Kn.		% Kn.		% Kn.		% Kn.		% Kn.
One	7	5.7	2	1.6	1	0.8	11	8.9	6	5.0	2	1.6
Two or More	2	1.6	0	0.0	0	0.0	1	0.8	1	0.8	0	0.0
Total Positive	9	7.3	2	1.6	1	0.8	12	9.7	7	5.8	2	1.6
None Reported	114	92.7	120	98.4	122	99.2	111	90.2	113	94.2	121	98.4
		% Tot.		% Tot.		% Tot.		% Tot.		% Tot.		% Tot.
Total Known	123	96.1	122	95.3	123	96.1	123	96.1	120	93.8	123	96.1
Unknown	5	3.9	6	4.7	5	3.9	5	3.9	8	6.2	5	3.9
TOTAL	128	100.0	128	100.0	128	100.0	128	100.0	128	100.0	128	100.0
Pooled #		% Kn.		% Kn.		% Kn.		% Kn.		% Kn.		% Kn.
One	7	4.9	2	1.4	2	1.4	14	9.7	6	4.3	2	1.4
Two or More	2	1.4	0	0.0	0	0.0	1	0.7	1	0.7	0	0.0
Total Positive	9	6.3	2	1.4	2	1.4	15	10.4	7	5.0	2	1.4
None Reported	134	93.7	140	98.6	141	98.6	129	89.6	134	95.0	142	98.6
		% Tot.		% Tot.		% Tot.		% Tot.		% Tot.		% Tot.
Total Known	143	95.3	142	94.7	143	95.3	144	96.0	141	94.0	144	96.0
Unknown	7	4.7	8	5.3	7	4.7	6	4.0	9	6.0	6	4.0
TOTAL	150	100.0	150	100.0	150	100.0	150	100.0	150	100.0	150	100.0

Included mothers of additional and questionable mongols and mothers of additional controls, as well as matched pairs.

MATERNAL FLUOROSCOPIC EXPOSURE x
Current Series

	Down's						Controls					
	Chest		Abdomen		Other		Chest		Abdomen		Other	
Number of sessions	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Matched Pairs		% Kn.		% Kn.		% Kn.		% Kn.		% Kn.		% Kn.
One	7	5.7	2	1.6	1	0.8	12	9.8	6	5.1	2	1.6
Two or More	2	1.6	0	0.0	0	0.0	0	0.0	1	0.8	2	1.6
Total Positive	9	7.3	2	1.6	1	0.8	12	9.8	7	5.9	4	3.2
None Reported	114	92.7	120	98.4	122	99.2	110	90.2	111	94.1	119	96.8
		% Tot.		% Tot.		% Tot.		% Tot.		% Tot.		% Tot.
Total Known	123	96.1	122	95.3	123	96.1	122	95.3	118	92.2	123	96.1
Unknown	5	3.9	6	4.7	5	3.9	6	4.7	10	7.8	5	3.9
TOTAL	128	100.0	128	100.0	128	100.0	128	100.0	128	100.0	128	100.0
Pooled (#)		% Kn.		% Kn.		% Kn.		% Kn.		% Kn.		% Kn.
One	7	4.9	2	1.4	2	1.4	15	10.5	6	4.3	2	1.4
Two or More	2	1.4	0	0.0	0	0.0	0	0.0	1	0.7	2	1.4
Total Positive	9	6.3	2	1.4	2	1.4	15	10.5	7	5.0	4	2.8
None Reported	134	93.7	140	98.6	141	98.6	128	89.5	132	95.0	140	97.2
		% Tot.		% Tot.		% Tot.		% Tot.		% Tot.		% Tot.
Total Known	143	95.3	142	94.7	143	95.3	143	95.3	139	92.7	144	96.0
Unknown	7	4.7	8	5.3	7	4.7	7	4.7	11	7.3	6	4.0
TOTAL	150	100.0	150	100.0	150	100.0	150	100.0	150	100.0	150	100.0

(#) Includes mothers of additional and questionable mongols and mothers of additional controls, as well as matched pairs.
x Prior to conception plus during year of conception, exact date unknown, could have been prior to or after conception *of index child.*

TABLE MED-4

MATERNAL THERAPEUTIC RADIATION BY SITE OF EXPOSURE: ONE OR MORE EXPOSURES

Current Series Matched Pairs

Condition or Area	Prior to Conception of Index				After Birth of Index			
	Down's		Controls		Down's		Controls	
	No.	%	No.	%	No.	%	No.	%
Skin, Warts, Birthmark	6	4.7	5	3.9	1	0.8	0	0
Tumors	1	0.8	2	1.6	0	0	1	0.8
Sinus/Adenoids	1	0.8	0	0	1	0.8	0	0
Bursitis	2	1.6	0	0	0	0	1	0.8
Rheumatism	0	0	0	0	1	0.8	0	0
Thyroid	0	0	0	0	0	0	0	0
Adrenals	0	0	0	0	0	0	0	0
Polycythemia	0	0	0	0	0	0	0	0
Other	2	1.6	0	0	1	0.8	1	0.8
Total Mothers	128		128		128		128	

% = % total mothers

TABLE MED 5A-i

TOTAL INTERVIEW DATA FOR MATERNAL FLUOROSCOPIC EXPOSURE PRIOR TO CONCEPTION OF THE INDEX CHILD BY MATERNAL AGE AT BIRTH OF IC AND NUMBER OF FLUOROSCOPIC SESSIONS

Current Series Matched Pairs

Maternal age at IC birth	Down's							Controls						
	Number of sessions							Number of sessions						
	One	2 or more	Total positive	None rept'd	Total known	Unk	Total	One	2 or more	Total positive	None rept'd	Total known	Unk	Total
≤19	0	0	0	6	6	0	6	1	0	1	5	6	0	6
20-24	0	0	0	17	17	1	18	2	0	2	15	17	0	17
25-29	1	1	2	16	18	0	18	0	1	1	18	19	1	20
30-34	1	0	1	22	23	2	25	4	1	5	19	24	1	25
35-39	0	2	2	34	36	2	38	4	2	6	26	32	4	36
40-44	4	1	5	16	21	1	22	3	0	3	19	22	2	24
45+	0	0	0	1	1	0	1	0	0	0	0	0	0	0
TOTAL	6	4	10	112	122	6	128	14	4	18	102	120	8	128
% known	4.9	3.3	8.2	91.8				11.7	3.3	15.0	85.0			
% total					95.3	4.7						93.8	6.2	

TABLE MED 5A-ii

TOTAL INTERVIEW DATA FOR MATERNAL FLUOROSCOPIC EXPOSURE PRIOR TO CONCEPTION OF THE INDEX CHILD
BY MATERNAL AGE AT BIRTH OF IC AND NUMBER OF FLUOROSCOPIC SESSIONS
Current Series Pooled #

Maternal age at IC birth	Down's							Controls						
	Number of sessions							Number of sessions						
	One	2 or more	Total positive	None rept'd	Total known	Unk	Total	One	2 or more	Total positive	None rept'd	Total known	Unk	Total
≤19	3	0	3	8	11	0	11	2	0	2	9	11	0	11
20-24	4	0	4	18	22	1	23	3	0	3	20	23	1	24
25-29	1	1	2	17	19	0	19	0	1	1	19	20	1	21
30-34	1	0	1	24	25	4	29	4	1	5	22	27	1	28
35-39	2	2	4	36	40	2	42	4	2	6	30	36	4	40
40-44	5	1	6	18	24	1	25	4	0	4	20	24	2	26
45+	0	0	0	1	1	0	1	0	0	0	0	0	0	0
TOTAL	16	4	20	122	142	8	150	17	4	21	120	141	9	150
% known	11.3	2.8	14.1	85.9				12.1	2.8	14.9	85.1			
% total					94.7	5.3						94.0	6.0	

Includes mothers of additional and questionable Down's cases and mothers of additional controls, as well as matched pairs.

TABLE MED 5B-i

TOTAL INTERVIEW DATA FOR MATERNAL FLUOROSCOPIC EXPOSURE PRIOR TO BIRTH OF THE INDEX CHILD
BY MATERNAL AGE AT BIRTH OF IC AND NUMBER OF FLUOROSCOPIC SESSIONS
Current Series Matched Pairs

Maternal age at IC birth	Down's							Controls						
	Number of sessions							Number of sessions						
	One	2 or more	Total positive	None rept'd	Total known	Unk	Total	One	2 or more	Total positive	None rept'd	Total known	Unk	Total
≤19	0	0	0	6	6	0	6	1	0	1	5	6	0	6
20-24	0	0	0	17	17	1	18	2	0	2	15	17	0	17
25-29	1	1	2	16	18	0	18	0	1	1	18	19	1	20
30-34	1	0	1	22	23	2	25	4	2	6	17	23	2	25
35-39	0	2	2	34	36	2	38	4	2	6	25	31	5	36
40-44	4	1	5	16	21	1	22	3	1	4	17	21	3	24
45+	0	0	0	1	1	0	1	0	0	0	0	0	0	0
TOTAL	6	4	10	112	122	6	128	14	6	20	97	117	11	128
% known	4.9	3.3	8.2	91.8				12.0	5.1	17.1	82.9			
% total					95.3	4.7						91.4	8.6	

TABLE MED 5B-ii

TOTAL INTERVIEW DATA FOR MATERNAL FLUOROSCOPIC EXPOSURE PRIOR TO BIRTH OF THE INDEX CHILD
BY MATERNAL AGE AT BIRTH OF IC AND NUMBER OF FLUOROSCOPIC SESSIONS
Current Series Pooled (#)

Maternal age at IC birth	Down's							Controls						
	Number of sessions							Number of sessions						
	One	2 or more	Total positive	None rept'd	Total known	Unk	Total	One	2 or more	Total positive	None rept'd	Total known	Unk	Total
≤19	0	0	0	11	11	0	11	2	0	2	9	11	0	11
20-24	0	0	0	22	22	1	23	3	0	3	20	23	1	24
25-29	1	1	2	17	19	0	19	0	1	1	19	20	1	21
30-34	1	0	1	24	25	4	29	4	2	6	20	26	2	28
35-39	1	2	3	37	40	2	42	4	2	6	29	35	5	40
40-44	4	1	5	19	24	1	25	4	1	5	18	23	3	26
45+	0	0	0	1	1	0	1	0	0	0	0	0	0	0
TOTAL	7	4	11	131	142	8	150	17	6	23	115	138	12	150
% known	4.9	2.8	7.7	92.3				12.3	4.3	16.7	83.3			
% total					94.7	5.3						92.0	8.0	

(#) Includes mothers of additional and questionable Down's cases and mothers of additional controls, as well as matched pairs.

ES AND CONTROLS BY EDUCATION OF PARENTS (FROM INTERVIEW)
Current Series

THERS		FATHERS			
Pooled#		Matched Pairs		Pooled#	
Down's %	Controls %	Down's %	Controls %	Down's %	Controls %
12.2	13.4	18.0	20.6	18.8	18.9
30.4	29.5	21.9	27.0	25.5	26.6
37.8	35.6	31.3	17.5	28.9	19.6
15.5	14.1	10.9	16.7	10.7	16.1
3.4	7.4	10.2	13.5	9.4	12.6
0.7	-	5.5	3.2	4.7	4.2
-	-	1.6	-	1.3	0.7
-	-	0.8	1.6	0.7	1.4
148	149	128	126	149	143
2(1.3)	1(0.7)	0(-)	2(1.6)	1(0.7)	7(4.7)
150	150	128	128	150	150

and questionable mongols and mothers and fathers of additional controls,

TABLE S-1

DISTRIBUTION OF CASES AND CONTROLS BY EDUCATION OF PARENTS (FROM INTERVIEW)
Current Series

	MOTHERS				FATHERS			
	Matched Pairs		Pooled (#)		Matched Pairs		Pooled (#)	
	Down's	Controls	Down's	Controls	Down's	Controls	Down's	Controls
Educational Level	%	%	%	%	%	%	%	%
Elementary or less	12.7	14.8	12.2	13.4	18.0	20.6	18.8	18.9
Elementary and some high school	28.6	26.6	30.4	29.5	21.9	27.0	25.5	26.6
High school graduate	38.1	35.2	37.8	35.6	31.3	17.5	28.9	19.6
Some college or post high school	15.9	14.8	15.5	14.1	10.9	16.7	10.7	16.1
College graduate	4.0	8.6	3.4	7.4	10.2	13.5	9.4	12.6
Graduate school but not doctorate	0.8	-	0.7	-	5.5	3.2	4.7	4.2
Doctorate other than M.D.	-	-	-	-	1.6	-	1.3	0.7
M.D.	-	-	-	-	0.8	1.6	0.7	1.4
Number Known	126	128	148	149	128	126	149	143
Number Unknown	2(1.6)	0(-)	2(1.3)	1(0.7)	0(-)	2(1.6)	1(0.7)	7(4.7)
Total	128	128	150	150	128	128	150	150

% - percent known
( )- percent total

(#) Includes mothers and fathers of additional and questionable mongols and mothers and fathers of additional controls, as well as matched pairs.

TABLE SO-1

DISTRIBUTION OF CASES AND CONTROLS BY OCCUPATION OF PARENTS (FROM INTERVIEW)
Current Series

Occupation	MOTHERS				FATHERS			
	Matched Pairs		Pooled #		Matched Pairs		Pooled #	
	Down's %	Controls %	Down's %	Controls %	Down's %	Controls %	Down's %	Controls %
None	62.5	55.2	62.0	56.2	0	0.8	0	0.7
Professional (M.D., dentistry, veterinary, etc.)	5.5	6.4	5.3	5.5	0.8	3.2	0.7	3.5
Other professional (clergymen, artists, etc.)	1.6	2.4	2.0	2.1	12.7	9.5	12.9	9.1
Managers, officials, proprietors	1.6	0.8	1.3	1.4	18.3	23.0	19.7	24.5
Clerical and sales workers	19.5	20.0	20.0	21.2	9.5	9.5	9.5	9.8
Craftsmen, repairmen, foremen	0.8	2.4	0.7	2.1	34.1	25.4	32.0	25.9
Operatives (auto, train, ship, mine, mfg., etc.)	0.8	4.0	1.3	3.4	15.1	19.8	15.0	18.2
Service workers and laborers (not farm or mine)	7.8	8.8	7.3	8.2	9.5	8.7	10.2	8.4
Number Known	128	125	150	146	126	126	147	143
Number Unknown	0(0)	3(2.2)	0(0)	4(2.7)	2(1.6)	2(1.6)	3(2.0)	7(4.7)
Total	128	128	150	150	128	128	150	150

% - percent known
( ) - percent total

Includes mothers and fathers of additional and questionable Down's cases and mothers and fathers of additional controls, as well as matched pairs.

TABLE S-2

DISTRIBUTION OF CASES AND CONTROLS BY RELIGIOUS PREFERENCE OF PARENTS (FROM INTERVIEW)

Current Series

	MOTHERS				FATHERS			
	Matched Pairs		Pooled #		Matched Pairs		Pooled #	
Religion	Down's %	Controls %	Down's %	Controls %	Down's %	Controls %	Down's %	Controls %
None	1.6	0	1.3	0	3.1	2.4	2.7	2.8
Roman Catholic	53.1	46.9	51.3	47.0	43.8	42.5	45.0	41.0
Jewish	1.6	3.9	1.3	3.4	2.3	3.9	2.0	3.5
Greek Orthodox	0	1.6	0	1.3	0	1.6	0	1.4
Protestant	43.8	46.1	45.3	47.0	50.8	48.8	50.3	50.7
Other	0	1.6	0.7	1.3	0	0.8	0	0.7
Number Known	128	128	150	149	128	127	149	144
Number Unknown	0(-)	0(-)	0(-)	1(0.7)	0(-)	1(0.8)	1(0.7)	6(4.0)
Total	128	128	150	150	128	128	150	150

% - percent known
( )- percent total

Includes mothers and fathers of additional and questionable Down's cases and mothers and fathers of additional controls, as well as matched pairs.

Please note:

The following masters of Tables MR-1 through MR-5 are the best we have. The original copies are not available.

TABLE MR-1

MATERNAL MARITAL HISTORY BEFORE MARRIAGE TO FATHER OF INDEX CHILD BY MATERNAL MEDICAL RADIATION EXPOSURE[x] (FROM INTERVIEW)
Current Series Matched Pairs

Marriages Prior to Father of IC	Total Mothers		Mothers With: No Radn.		Any Radn.		Diag. X-Ray		Thera.		Fluoro.		Diag. Thera.		Diag. Fluoro.		Diag. Thera. Fluoro.		Unknown Radn.	
	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%
Down's																				
None	108	84.4	34	79.1	73	89.0	54	88.5	7	100.0	2	100.0	3	100.0	7	87.5	0	0	1	33.3
One	19	14.8	9	20.9	8	9.8	6	9.8	0	0	0	0	0	0	1	12.5	1	100.0	2	66.7
>One	1	0.8	0	0	1	1.2	1	1.6	0	0	0	0	0	0	0	0	0	0	0	0
Total	128	100.0	43	100.0	82	100.0	61	100.0	7	100.0	2	100.0	3	100.0	8	100.0	1	100.0	3	100.0
Controls																				
None	111	86.7	37	88.1	71	85.5	48	81.4	1	100.0	3	100.0	5	100.0	12	92.3	2	100.0	3	100.0
One	15	11.7	4	9.5	11	13.3	10	16.9	0	0	0	0	0	0	1	7.7	0	0	0	0
>One	2	1.6	1	2.4	1	1.2	1	1.7	0	0	0	0	0	0	0	0	0	0	0	0
Total	128	100.0	42	100.0	83	100.0	59	100.0	1	100.0	3	100.0	5	100.0	13	100.0	2	100.0	3	100.0

[x]Medical radiation prior to conception or during first month of conception or exact date unknown during that year of conception.

TABLE MR2

TOTAL MARITAL HISTORY OF MOTHERS BY MATERNAL MEDICAL RADIATION EXPOSURE^{x} (FROM INTERVIEW)
Current Series Matched Pairs

Marriages Any Time	Total Mothers		Mothers With: No Radn.		Any Radn.		Diag. X-Ray		Thera.		Fluoro.		Diag. Thera.		Diag. Fluoro.		Diag. Thera. Fluoro.		Unknown Radn.	
	#	%	#	%	#	%	#	%	#	%	#	%	%	%	#	%	#	%	#	%
Down's Cases																				
None	1	0.8	0	0	1	1.2	1	1.6	0	0	0	0	0	0	0	0	0	0	0	0
One	107	83.6	34	79.1	72	87.8	53	86.9	7	100.0	2	100.0	3	100.0	7	87.5	0	0	1	33.3
>One	20	15.6	9	20.9	9	11.0	7	11.5	0	0	0	0	0	0	1	12.5	1	100.0	2	66.7
Total	128	100.0	43	100.0	82	100.0	61	100.0	7	100.0	2	100.0	3	100.0	8	100.0	1	100.0	3	100.0
Controls																				
None	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
One	109	85.2	36	85.7	70	84.3	47	79.7	1	100.0	3	100.0	5	100.0	12	92.3	2	100.0	3	100.0
>One	19	14.8	6	14.3	13	15.7	12	20.3	0	0	0	0	0	0	1	7.7	0	0	0	0
Total	128	100.0	42	100.0	83	100.0	59	100.0	1	100.0	3	100.0	5	100.0	13	100.0	2	100.0	3	100.0

^{x}Medical radiation prior to conception or during first month of conception or exact date unknown during that year of conception.

TABLE MR-3

PREGNANCY HISTORY IN MOTHERS OF CHILDREN WITH DOWN'S SYNDROME AND IN MOTHERS OF CONTROLS
BY MATERNAL AGE AND BY TIME RELATIONSHIP TO INDEX CHILD
Current Series Matched Pairs
(with Totals for Original and Combined Series)

	Mothers		Prior to Index Child						Subsequent to Index Child					
			Total Pregnancies		Abortions and Stillbirths				Total Pregnancies		Abortions and Stillbirths			
Age					Down's		Controls				Down's		Controls	
Groups	Down's	Controls	Down's	Controls	Number	Percent	Number	Percent	Down's	Controls	Number	Percent	Number	Percent
<20	6	6	3	0	0	0	0	0	11	8	3	27.27	0	0
20-24	18	17	29	13	5	17.24	1	7.69	14	15	5	35.71	2	13.33
25-29	18	20	34	48	5	14.71	9	18.75	15	9	4	26.67	2	22.22
30-34	25	25	53	85	1	1.89	9	10.59	9	7	3	33.33	1	14.29
35-39	38	36	134	141	25	18.66	21	14.89	9	9	4	44.44	2	22.22
40-44	22	24	106	131	23	21.70	22	16.79	0	3	0	0	2	66.67
45-49	1	0	5	0	0	0	0	0	0	0	0	0	0	0
50+	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TOTAL: Cur.	128	128	364	418	59	16.21	62	14.83	58	51	19	32.76	9	17.65
TOTAL: Orig.	216	216	527	517	84	15.9	76	14.7	176	188	28	15.9	31	16.5
TOTAL: Comb.	344	344	891	935	143	16.1	138	14.8	234	239	47	20.1	40	16.7

Cur. = Current Series
Orig. = Original Series
Comb. = Combined Series

TABLE MR-4

PREGNANCY HISTORY IN MOTHERS OF CHILDREN WITH DOWN'S SYNDROME AND IN MOTHERS OF CONTROLS
BY MATERNAL AGE AND TIME RELATIONSHIP TO INDEX CHILD
Current Series Pooled #

			Prior to Index Child						Subsequent to Index Child					
			Total Pregnancies		Abortions and Stillbirths				Total Pregnancies		Abortions and Stillbirths			
Age Groups	Down's	Controls	Down's	Controls	Down's		Controls		Down's	Controls	Down's		Controls	
					Number	Percent	Number	Percent			Number	Percent	Number	Percent
< 20	11	11	3	0	0	0	0	0	18	13	5	27.78	0	0
20-24	23	24	34	22	7	20.59	2	9.09	22	18	7	31.82	2	11.11
25-29	19	21	35	50	5	14.29	9	18.00	15	9	4	26.67	2	22.22
30-34	29	28	69	92	6	8.70	9	9.78	11	10	3	27.27	1	10.00
35-39	42	40	151	155	27	17.88	21	13.55	10	11	4	40.00	3	27.27
40-44	25	26	118	141	27	22.88	25	17.73	1	3	0	0	2	66.67
45-49	1	0	5	0	0	0	0	0	0	0	0	0	0	0
50+	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total: Cur.	150	150	415	456	72	17.35	66	14.47	77	64	23	29.87	10	15.63

Includes mothers of additional and questionable Down's cases and mothers of additional controls, as well as matched pairs.

TABLE MR-5

MENSTRUAL HISTORY OF MOTHERS OF CHILDREN WITH DOWN'S SYNDROME AND OF CONTROL CHILDREN
Current Series Matched Pairs

Data	Down's	Controls	Based on: N Down's	N Controls	P Value
Mean age at menarche (years)	12.54	12.73	123	124	>.30
Mean age at menopause (years)	39.93	39.89	15	18	>.90
Still menstruating (%)	88.19	85.71	127	126	.69
Operative menopause (%)	7.87	11.90	127	126	.40
Always regular period (%)	67.72	64.57	127	127	.69
Mean duration of menstrual period (days)▲	5.15	5.10	121	119	>.70
Mean interval between periods (days)▲	27.97	28.12	116	114	>.50

▲ Excluding irregular and unknown

TABLE T-1

MATERNAL THYROID HISTORY PRIOR TO CONCEPTION OF

Current Series

	Thyroid Medication		Thyroid Surgery		Thyroid Treatment		
	Down's Cases	Controls	Down's Cases	Controls	Down's Cases	Controls	Dov Ca
Mothers of:							
Matched Pairs							
No	118	118	128	128	126	123	12
Yes	10	10	0	0	2	5	
Total Known	128	128	128	128	128	128	12
Total Unknown	0	0	0	0	0	0	
Total	128	128	128	128	128	128	12
Pooled (#)							
No	139	137	150	149	148	143	14
Yes	11	12	0	0	2	6	
Total Known	150	149	150	149	150	149	15
Total Unknown	0	1	0	1	0	1	
Total	150	150	150	150	150	150	15

(#) Includes mothers of additional and questionable mongols and mothers of additional controls, a

MATERNAL THYROID HISTORY PRIOR TO CONCEPTION OF INDEX CHILD

Current Series

Thyroid Surgery		Thyroid Treatment		Thyroid Tests		Thyroid Disease	
Down's Cases	Controls	Down's Cases	Controls	Down's Cases	Controls	Down's Cases	Controls
128	128	126	123	127	126	121	122
0	0	2	5	1	2	7	5
128	128	128	128	128	128	128	127
0	0	0	0	0	0	0	1
128	128	128	128	128	128	128	128
150	149	148	143	149	147	142	141
0	0	2	6	1	2	7	7
150	149	150	149	150	149	149	148
0	1	0	1	0	1	1	2
150	150	150	150	150	150	150	150

tionable mongols and mothers of additional controls, as well as matched pairs.

TABLE T-2

MATERNAL THYROID HISTORY[x]

Current Series

	Thyroid Medication		Thyroid Surgery		Thyroid Treatment		Do
	Down's Cases	Controls	Down's Cases	Controls	Down's Cases	Controls	Ca
Mothers of:							
Matched Pairs							
No	117	117	128	128	126	123	12
Yes	11	11	0	0	2	5	
Total Known	128	128	128	128	128	128	12
Total Unknown	0	0	0	0	0	0	
Total	128	128	128	128	128	128	12
Pooled #							
No	137	135	150	149	148	143	14
Yes	13	14	0	0	2	6	
Total Known	150	149	150	149	150	149	15
Total Unknown	0	1	0	1	0	1	
Total	150	150	150	150	150	150	15

x Thyroid history prior to conception plus during year of conception, exact date unknown, could index child.

Includes mothers of additional and questionable mongols and mothers of additional controls, as

MATERNAL THYROID HISTORY[x]

Current Series

Thyroid Surgery		Thyroid Treatment		Thyroid Tests		Thyroid Disease	
Down's Cases	Controls	Down's Cases	Controls	Down's Cases	Controls	Down's Cases	Controls
128	128	126	123	127	125	120	122
0	0	2	5	1	3	8	5
128	128	128	128	128	128	128	127
0	0	0	0	0	0	0	1
128	128	128	128	128	128	128	128
150	149	148	143	149	146	141	140
0	0	2	6	1	3	8	8
150	149	150	149	150	149	149	148
0	1	0	1	0	1	1	2
150	150	150	150	150	150	150	150

ring year of conception, exact date unknown, could have been before or after conception of

ble mongols and mothers of additional controls, as well as matched pairs.

KMH

MATERNAL MEDICAL HISTORY (FROM INTERVIEW)

(Current Series)

Diseases/Conditions by Time Relative to Conception of Index

Note: Tables MH-1 through MH-15 were extracted directly from computer printouts, and consequently indicate tabulations only for cells in which there were 1 or more subjects. In addition, the cells included vary from table to table. The key to the codes used is given below.

Key to Codes on Tables MH-1 - MH-15

Subjects = Mothers of:

CURR CASE	=	Down's cases in Current Series
CURR CONT	=	Controls in Current Series
ADDITIONAL	=	Additional subjects Down's cases or controls
QUESTIONABLE	=	Questionable Down's cases

Information =

Responses to questions as to this condition and its time relative to conception of index child

0 = Never or not mentioned
1 = Yes, prior to conception of index child
2 = Yes, during year of conception, exact date unknown, could have been before or after conception of index child
3 = Yes, after conception of index child, but during pregnancy
4 = Yes, after birth of index child
5 = Yes, time unknown
9 = Unknown

NOTE: Tables derived from direct reproduction of printouts with identifying labelling for clarity.

Please note:

There are no originals of pp. 157-163 (Tables MH1-MH15). These were taken from printouts.

TABLE MH1. MATERNAL HISTORY OF DIABETES — CURRENT SERIES

	POOLED	'MATCHED PAIRS'	ADDITIONAL	QUESTIONABLE
	300	256	35	9
CASES				
None	149	127	13	9
Prior to Conception	1	1	-	-
TOTAL	150	128	13	9
CONTROLS				
None	148	127	21	-
Prior to Conception	1	1	-	-
Unknown	1	-	1	-
TOTAL	150	128	22	-

See Key to MH Tables

TABLE MH 2. MATERNAL HISTORY OF DISORDERS OF ADRENAL GLANDS — CURRENT SERIES

	POOLED	'MATCHED PAIRS'	ADDITIONAL	QUESTIONABLE
	300	256	35	9
CASES				
None	150	128	13	9
CONTROLS				
None	149	128	21	-
Unknown	1	-	1	-
TOTAL	150	128	22	-

See Key to MH Tables

TABLE MH3. MATERNAL HISTORY OF LIVER DISEASE — CURRENT SERIES

	POOLED	'MATCHED PAIRS'	ADDITIONAL	QUESTIONABLE
	300	256	35	9
CASES				
None	147	126	12	9
Prior to Conception	2	1	1	-
Time Unknown	1	1	-	-
TOTAL	150	128	13	9
CONTROLS				
None	145	124	21	-
Prior to Conception	2	2	-	-
After Birth	1	1	-	-
Unknown	2	1	1	-
TOTAL	150	128	22	-

See Key to MH Tables

TABLE MH4. MATERNAL HISTORY OF NEPHRITIS — CURRENT SERIES

	POOLED	'MATCHED PAIRS'	ADDITIONAL	QUESTIONABLE
	300	256	35	9
CASES				
None	130	110	12	8
Prior to Conception	11	10	1	-
Exact Date Unknown	1	1	-	-
After Conception	3	2	-	1
After Birth	5	5	-	-
TOTAL	150	128	13	9
CONTROLS				
None	132	114	18	-
Prior to Conception	7	5	2	-
Exact Date Unknown	2	1	1	-
After Birth	7	7	-	-
Unknown	2	1	1	-
TOTAL	150	128	22	-

See Key to MH Tables

TABLE MH5. MATERNAL HISTORY OF TUBERCULOSIS — CURRENT SERIES

	POOLED	'MATCHED PAIRS'	ADDITIONAL	QUESTIONABLE
	300	256	35	9
CASES				
None	149	127	13	9
Prior to Conception	1	1	-	-
TOTAL	150	128	13	9
CONTROLS				
None	148	127	21	-
Prior to Conception	1	1	-	-
Unknown	1	-	1	-
TOTAL	150	128	22	-

See Key to MH Tables

AD-A061 593 JOHNS HOPKINS UNIV BALTIMORE MD SCHOOL OF HYGIENE A--ETC F/G 6/18
PARENTAL RADIATION AND DOWN'S SYNDROME, WITH PARTICULAR ATTENTI--ETC(U)
JUN 76 B H COHEN DADA17-69-C-0154

UNCLASSIFIED NL

3 OF 5

AD
A061 593

593

159

TABLE MH6. MATERNAL HISTORY OF REPRODUCTIVE ORGAN DISORDERS — CURRENT SERIES

	POOLED	'MATCHED PAIRS'	ADDITIONAL	QUESTIONABLE
CASES	300	256	35	9
None	112	95	9	8
Prior to Conception	22	20	2	-
After Conception	1	1	-	-
After Birth	14	11	2	1
Unknown	1	1	-	-
TOTAL	150	128	13	9
CONTROLS				
None	109	91	18	-
Prior to Conception	19	18	1	-
After Conception	2	2	-	-
After Birth	19	17	2	-
Unknown	1	-	1	-
TOTAL	150	128	22	-

See Key to MH Tables

TABLE MH7. MATERNAL HISTORY OF RHEUMATIC HEART DISEASE — CURRENT SERIES

	POOLED	'MATCHED PAIRS'	ADDITIONAL	QUESTIONABLE
CASES	300	256	35	9
None	147	125	13	9
Prior to Conception	2	2	-	-
Unknown	1	1	-	-
TOTAL	150	128	13	9
CONTROLS				
None	142	121	21	-
Prior to Conception	4	4	-	-
After Birth	1	1	-	-
Unknown	3	2	1	-
TOTAL	150	128	22	-

See Key to MH Tables

TABLE MH8. MATERNAL HISTORY OF CANCER — CURRENT SERIES

	POOLED	'MATCHED PAIRS'	ADDITIONAL	QUESTIONABLE
CASES	300	256	35	9
None	147	125	13	9
After Birth	2	2	-	-
Unknown	1	1	-	-
TOTAL	150	128	13	9
CONTROLS				
None	145	124	21	-
Prior to Conception	1	1	-	-
After Conception	1	1	-	-
After Birth	1	1	-	-
Unknown	2	1	1	-
TOTAL	150	128	22	-

See Key to MH Tables

TABLE MH9. MATERNAL HISTORY OF NON-MALIGNANT TUMORS — CURRENT SERIES

	POOLED	'MATCHED PAIRS'	ADDITIONAL	QUESTIONABLE
CASES	300	256	35	9
None	115	97	10	8
Prior to Conception	21	20	1	-
Exact Date Unknown	2	2	-	-
After Conception	1	1	-	-
After Birth	9	6	2	1
Time Unknown	1	1	-	-
Unknown	1	1	-	-
TOTAL	150	128	13	9
CONTROLS				
None	108	93	15	-
Prior to Conception	23	21	2	-
After Conception	2	2	-	-
After Birth	14	11	3	-
Time Unknown	1	1	-	-
Unknown	2	-	2	-
TOTAL	150	128	22	-

See Key to MH Tables

TABLE MH10. MATERNAL HISTORY OF CHILDHOOD DISEASES CURRENT SERIES

	POOLED	'MATCHED PAIRS'	ADDITIONAL	QUESTIONABLE
CASES	300	256	35	9
None	2	2	-	-
Prior to Conception	125	105	11	9
Exact Date Unknown	1	1	-	-
After Birth	3	3	-	-
Time Unknown	9	9	-	-
Unknown	10	8	2	-
TOTAL	150	128	13	9
CONTROLS				
None	7	6	1	-
Prior to Conception	121	102	19	-
Time Unknown	10	10	-	-
Unknown	12	10	2	-
TOTAL	150	128	22	-

See Key to MH Tables

TABLE MH11. MATERNAL HISTORY OF ANEMIA & OTHER BLOOD DISORDERS CURRENT SERIES

	POOLED	'MATCHED PAIRS'	ADDITIONAL	QUESTIONABLE
CASES	300	256	35	9
None	110	93	11	6
Prior to Conception	28	26	1	1
Exact Date Unknown	4	3	1	-
After Conception	1	1	-	-
After Birth	6	4	-	2
Unknown	1	1	-	-
TOTAL	150	128	13	9
CONTROLS				
None	118	103	15	-
Prior to Conception	20	17	3	-
Exact Date Unknown	2	2	-	-
After Conception	1	-	1	-
After Birth	3	2	1	-
Time Unknown	4	3	1	-
Unknown	2	1	1	-
TOTAL	150	128	22	-

See Key to MH Tables

TABLE MH12. MATERNAL HISTORY OF LEUKEMIA — CURRENT SERIES

	POOLED	'MATCHED PAIRS'	ADDITIONAL	QUESTIONABLE
CASES	299	256	35	8
None	149	128	13	8
CONTROLS				
None	149	128	21	-
Unknown	1	-	1	-
TOTAL	150	128	22	-

See Key to MH Tables

TABLE MH13. MATERNAL HISTORY OF HYPERTENSION — CURRENT SERIES

	POOLED	'MATCHED PAIRS'	ADDITIONAL	QUESTIONABLE
CASES	299	256	35	8
None	135	114	13	8
Prior to Conception	3	3	-	-
After Conception	1	1	-	-
After Birth	7	7	-	-
Unknown	3	3	-	-
TOTAL	149	128	13	8
CONTROLS				
None	136	115	21	-
Prior to Conception	4	4	-	-
Exact Date Unknown	1	1	-	-
After Birth	5	5	-	-
Time Unknown	1	1	-	-
Unknown	3	2	1	-
TOTAL	150	128	22	-

See Key to MH Tables

TABLE MH14. MATERNAL HISTORY OF CONVULSIONS OR EPILEPSY — CURRENT SERIES

	POOLED	'MATCHED PAIRS'	ADDITIONAL	QUESTIONABLE
CASES	299	256	35	8
None	143	123	12	8
Prior to Conception	3	3	-	-
After Birth	2	1	1	-
Unknown	1	1	-	-
TOTAL	149	128	13	8
CONTROLS				
None	142	122	20	-
Prior to Conception	6	5	1	-
After Birth	1	1	-	-
Unknown	1	-	1	-
TOTAL	150	128	22	-

See Key to MH Tables

TABLE MH 15. MATERNAL HISTORY OF VISUAL & HEARING DEFECTS CURRENT SERIES

	POOLED	'MATCHED PAIRS'	ADDITIONAL	QUESTIONABLE
CASES	299	256	35	8
None	141	121	12	8
Prior to Conception	5	4	1	-
After Birth	2	2	-	-
Time Unknown	1	1	-	-
TOTAL	149	128	13	8
CONTROLS				
None	144	124	20	-
Prior to Conception	5	4	1	-
Unknown	1	-	1	-
TOTAL	150	128	22	-

See Key to MH Tables

TABLE CS-1

CHROMOSOME STUDY GROUPS OF RADAR-MICROWAVE EXPOSED AND UNEXPOSED FATHERS BY SERIES AND INDEX SOURCE

MATCHED PAIRS			Original Series	Current Series	Combined	Fathers Exposed & Unexposed
Exposed fathers of:	vs	Unexposed fathers of:				
Down's	vs	Controls	8	8	16	
Controls	vs	Down's	4	9	13	
Down's	vs	New Matches	6	3	9	
Controls	vs	New Matches	11	3	14	
New Matches	vs	New Matches	3	0	3	
Total Pairs			32	23	55	
Total Fathers						110
Near exposed fathers of:	vs	Unexposed fathers of:				
Down's	vs	Controls	2	1	3	
Controls	vs	Down's	0	1	1	
Down's	vs	New Matches	1	0	1	
Controls	vs	New Matches	2	0	2	
New Matches	vs	New Matches	0	0	0	
Total Pairs			5	2	7	
Total Fathers						14
UNMATCHED FATHERS OF:						
Exposed Down's			3	2	5	
Exposed Controls			0	4	4	
Exposed New Matches			3	2	5	
Near Exposed Down's			2	0	2	
Near Exposed Controls			5	0	5	
Near Exposed New Matches			4	1	5	
Unexposed Down's			0	1	1	
Unexposed Controls			7	0	7	
Unexposed New Matches			2	2	4	
Total Unmatched Fathers			26	12	38	38
GRAND TOTAL						162

Exposed Fathers		Unexposed Fathers	
Matched	62	Matched	62
Unmatched	26	Unmatched	12
Total	88	Total	74

TABLE CS-2A

SUMMARY OF CHROMOSOMAL FINDINGS ON FATHERS BY RADAR-MICROWAVE EXPOSU
Includes Down's, Controls, and New Match Fathers from Original and Curr

Radar - Microwave Status	D		A		B		C		AB		AC		BC		3
	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#
TOTALS	71	44.7	2	1.3	37	23.3	26	16.4	2	1.3	1	0.6	16	10.1	4
Matched Pairs															
Exposed	22	40.0	1	1.8	10	18.2	11	20.0	1	1.8	1	1.8	6	10.9	3
Unexposed	25	46.3	1	1.9	15	27.8	6	11.1	0	0.0	0	0.0	6	11.1	1
Near Exposure	3	42.9	0	0.0	0	0.0	3	42.9	0	0.0	0	0.0	1	14.3	0
Unexposed Matches	5	71.4	0	0.0	2	28.6	0	0.0	0	0.0	0	0.0	0	0.0	0
Unmatched															
Exposed	5	35.7	0	0.0	5	35.7	2	14.3	1	7.1	0	0.0	1	7.1	0
Near Exposure	6	50.0	0	0.0	2	16.7	2	16.7	0	0.0	0	0.0	2	16.7	0
Unexposed	6	60.0	0	0.0	2	20.0	2	20.0	0	0.0	0	0.0	0	0.0	0
Pooled Groups															
Exposed (Match + Unmatch)	27	39.1	1	1.4	15	21.7	13	18.8	2	2.9	1	1.4	7	10.0	3
Matched Only Exposed + Near Exp.	25	40.3	1	1.6	10	16.1	14	22.6	1	1.6	1	1.6	7	11.3	3
All types Exposed+	36	40.9	1	1.1	17	19.3	18	20.5	2	2.3	1	1.1	10	11.4	3
All Unexposed	36	50.7	1	1.4	19	26.8	8	11.3	0	0.0	0	0.0	6	8.5	1

CLASSIFICATION OF CHROMOSOMAL FINDINGS - NORMAL AND VARIANT TYPE

Category D - Normal
Category A - Cytological abnormality or variation including: long #2, long short arm G, secondary co uncoiled #1, etc.
Category B - Abnormality that may be due to a mutagenic agent including: quadriradials, endoreduplic dicentric, double chromatid breaks, etc.
Category C - "Abnormality" that may be due to mechanical or technical error including: gaps or singl

TABULATION OF INDIVIDUAL CATEGORIES AND COMBINATIONS

D,A,B,C respectively	only the 1 type designated	Any A	A only, or i
AB,AC,BC	both the types designated	Any B	B " , "
ABC	all 3 types A+B+C types	Any C	C " , "
1 deviant type only	A or B or C	Any A and/or B	A &/or B alo
2 types	2 deviant types other than D (A+B or A+C or B+C)	Any A and/or C	A or C alone
		Any B and/or C	B or C "
Any 1 type	D only or A only or B only or C only	A and/or B and/or C	A or B or C

% Based on number of persons with at least one successful culture. + Matched, Unmatched, Exposed

Mutually exclusive chromosomal categories. A father with a successful culture is classified in o an individual defect "A only", "B only", or in a combination "AB".

OF CHROMOSOMAL FINDINGS ON FATHERS BY RADAR-MICROWAVE EXPOSURE STATUS ⊗
own's, Controls, and New Match Fathers from Original and Current Series

A		B		C		AB		AC		BC		3 TYPES ABC		CULTURE FAILURE		SUCCESS		TOTAL
#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#
2	1.3	37	23.3	26	16.4	2	1.3	1	0.6	16	10.1	4	2.5	3	1.9	159	98.1	162
1	1.8	10	18.2	11	20.0	1	1.8	1	1.8	6	10.9	3	5.5	0	0.0	55	100.0	55
1	1.9	15	27.8	6	11.1	0	0.0	0	0.0	6	11.1	1	1.9	1	1.8	54	98.2	55
0	0.0	0	0.0	3	42.9	0	0.0	0	0.0	1	14.3	0	0.0	0	0.0	7	100.0	7
0	0.0	2	28.6	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	7	100.0	7
0	0.0	5	35.7	2	14.3	1	7.1	0	0.0	1	7.1	0	0.0	0	0.0	14	100.0	14
0	0.0	2	16.7	2	16.7	0	0.0	0	0.0	2	16.7	0	0.0	0	0.0	12	100.0	12
0	0.0	2	20.0	2	20.0	0	0.0	0	0.0	0	0.0	0	0.0	2	16.7	10	83.3	12
1	1.4	15	21.7	13	18.8	2	2.9	1	1.4	7	10.0	3	4.3	0	0.0	69	100.0	69
1	1.6	10	16.1	14	22.6	1	1.6	1	1.6	7	11.3	3	4.8	0	0.0	62	100.0	62
1	1.1	17	19.3	18	20.5	2	2.3	1	1.1	10	11.4	3	3.4	0	0.0	88	100.0	88
1	1.4	19	26.8	8	11.3	0	0.0	0	0.0	6	8.5	1	1.4	3	4.1	71	95.9	74

SIFICATION OF CHROMOSOMAL FINDINGS - NORMAL AND VARIANT TYPES

ariation including: long #2, long short arm G, secondary constriction #1, fragile #16,

to a mutagenic agent including: quadriradials, endoreduplication, fragmented chromosomes, breaks, etc.

e to mechanical or technical error including: gaps or single chromatid breaks.

TABULATION OF INDIVIDUAL CATEGORIES AND COMBINATIONS

type designated	Any A...............A only, or in combination with B and/or C
ypes designated	Any B...............B " , " " " " A and/or C
s A+B+C types	Any C...............C " , " " " " A and/or B
C	Any A and/or B.......A &/or B alone or in any combination of other types
types other than D	Any A and/or C.......A or C alone or in any combination of other types
C or B+C)	Any B and/or C.......B or C " " " " " " " "
A only or B only or C only	A and/or B and/or C..A or B or C alone or in any " " " "

st one successful culture. + Matched, Unmatched, Exposed and Near.

ies. A father with a successful culture is classified in only one chromosomal category - e.g. with ", or in a combination "AB".

TABLE CS-2B

SUMMARY OF CHROMOSOMAL FINDINGS ON FATHERS BY RADAR-MICROWAVE
Includes Down's, Controls, and New Match Fathers from Original

Radar - Microwave Status	3 TYPES ABC		TWO TYPES		ANY ONE TYPE ONLY		1 TYPE ONLY-A, B, or C		ANY A		ANY B		ANY C		A
	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#
TOTALS	4	2.5	19	11.9	136	85.5	65	40.9	9	5.7	59	37.1	47	29.6	62
Matched Pairs															
Exposed	3	5.5	8	14.5	44	80.0	22	40.0	6	10.9	20	36.4	21	38.2	22
Unexposed	1	1.9	6	11.1	47	87.0	22	40.7	2	3.7	22	40.7	13	24.1	23
Near Exposure	0	0.0	1	14.3	6	85.7	3	42.9	0	0.0	1	14.3	4	57.1	1
Unexposed Matches	0	0.0	0	0.0	7	100.0	2	28.6	0	0.0	2	28.6	0	0.0	2
Unmatched															
Exposed	0	0.0	2	14.3	12	85.7	7	50.0	1	7.1	7	50.0	3	21.4	7
Near Exposure	0	0.0	2	16.7	10	83.3	4	33.3	0	0.0	4	33.3	4	33.3	4
Unexposed	0	0.0	0	0.0	10	100.0	4	40.0	0	0.0	2	20.0	2	20.0	2
Pooled Groups															
Exposed (Match + Unmatch)	3	4.3	10	14.5	56	81.2	29	42.0	7	10.1	27	39.1	24	34.8	29
Matched Only Exposed + Near Exp.	3	4.8	9	14.5	50	80.6	25	40.3	6	9.7	21	33.9	25	40.3	23
All types Exposed +	3	3.4	13	14.8	72	81.8	36	40.1	7	8.0	32	36.4	32	36.4	34
All Unexposed	1	1.4	6	8.5	64	90.1	28	39.4	2	2.8	26	36.6	15	21.1	27

CLASSIFICATION OF CHROMOSOMAL FINDINGS - NORMAL AND VARIANT TYPES

Category D - Normal
Category A - Cytological abnormality or variation including: long #2, long short arm G, secondary co
uncoiled #1, etc.
Category B - Abnormality that may be due to a mutagenic agent including: quadriradials, endoreduplic
dicentric, double chromatid breaks, etc.
Category C - "Abnormality" that may be due to mechanical or technical error including: gaps or singl

TABULATION OF INDIVIDUAL CATEGORIES AND COMBINATIONS

D,A,B,C respectively.........	only the 1 type designated	Any A................	A only, or in
AB,AC,BC.....................	both the types designated	Any B................	B " , " "
ABC..........................	all 3 types A+B+C types	Any C................	C " , " "
1 deviant type only..........	A or B or C	Any A and/or B.......	A &/or B alon
2 types......................	2 deviant types other than D (A+B or A+C or B+C)	Any A and/or C.......	A or C alone
		Any B and/or C.......	B or C "
Any 1 type...................	D only or A only or B only or C only	A and/or B and/or C..	A or B or C a

% Based on number of persons with at least one successful culture. + Matched, Unmatched, Exposed a

x Mutually exclusive chromosomal categories. A father with a successful culture is classified in onl
an individual defect "A only", "B only", or in a combination "AB".

(X)

NDINGS ON FATHERS BY RADAR-MICROWAVE EXPOSURE STATUS
and New Match Fathers from Original and Current Series

PE -A, r C	ANY A		ANY B		ANY C		ANY A&/orB		ANY A&/orC		ANY B&/orC		A&/or B&/orC		CULTURE FAILURE		CULTURE SUCCESS		TOTAL
%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#
0.9	9	5.7	59	37.1	47	29.6	62	39.0	51	32.1	86	54.1	88	55.3	3	1.9	159	98.1	162
0.0	6	10.9	20	36.4	21	38.2	22	40.0	23	41.8	32	58.2	33	60.0	0	0.0	55	100.0	55
0.7	2	3.7	22	40.7	13	24.1	23	42.6	14	25.9	28	51.9	29	53.7	1	1.8	54	98.2	55
2.9	0	0.0	1	14.3	4	57.1	1	14.3	4	57.1	4	57.1	4	57.1	0	0.0	7	100.0	7
8.6	0	0.0	2	28.6	0	0.0	2	28.6	0	0.0	2	28.6	2	28.6	0	0.0	7	100.0	7
0.0	1	7.1	7	50.0	3	21.4	7	30.0	4	28.6	9	64.3	9	64.3	0	0.0	14	100.0	14
3.3	0	0.0	4	33.3	4	33.3	4	33.3	4	33.3	6	50.0	6	50.0	0	0.0	12	100.0	12
0.0	0	0.0	2	20.0	2	20.0	2	20.0	2	20.0	4	40.0	4	40.0	2	16.7	10	83.3	12
2.0	7	10.1	27	39.1	24	34.8	29	42.0	27	39.1	41	54.4	42	60.9	0	0.0	69	100.0	69
0.3	6	9.7	21	33.9	25	40.3	23	37.1	27	43.5	36	58.1	37	59.7	0	0.0	62	100.0	62
0.1	7	8.0	32	36.4	32	36.4	34	38.6	35	39.8	51	58.0	52	59.1	0	0.0	88	100.0	88
.4	2	2.8	26	36.6	15	21.1	27	38.0	16	22.5	34	47.9	35	49.3	3	4.1	71	95.9	76

FINDINGS - NORMAL AND VARIANT TYPES

#2, long short arm G, secondary constriction #1, fragile #16,

uding: quadriradials, endoreduplication, fragmented chromosomes,

cal error including: gaps or single chromatid breaks.

L CATEGORIES AND COMBINATIONS

Any A................A only, or in combination with B and/or C
Any B................B " , " " " " A and/or C
Any C................C " , " " " " A and/or B
Any A and/or B.......A &/or B alone or in any combination of other types
Any A and/or C.......A or C alone or in any combination of other types
Any B and/or C.......B or C " " " " " " " "
A and/or B and/or C..A or B or C alone or in any " " " "

\+ Matched, Unmatched, Exposed and Near.

essful culture is classified in only one chromosomal category - e.g. with
".

TABLE CS3

SUMMARY OF CHROMOSOMAL VARIANTS IN CATEGORY "A"⊙ BY APPEARANCE IN

	Total Fathers	Failed Cultures	Long #2's (A) Code "1"	Code "2"	Code "3"	Code "4"	Code "5"	Code "6"	Code "7"	Fragile #16 (A Code "1"	Code "2"	Code "3"	Code "4"	Co "5
MATCHED PAIRS														
Exposed	55	0	1	0	0	1	0	0	53	0	0	0	0	[illegible]
Unexposed	55	1	0	0	0	0	0	0	54	0	0	1	0	[illegible]
Near Exposure	7	0	0	0	0	0	0	0	7	0	0	0	0	[illegible]
Unexposed	7	0	0	0	0	0	0	0	7	0	0	0	0	[illegible]
UNMATCHED														
Exposed	14	0	0	0	0	0	0	0	14	0	0	1	0	[illegible]
Near Exposure	12	0	0	0	0	0	0	0	12	0	0	0	0	[illegible]
Unexposed	12	2	0	0	0	0	0	0	10	0	0	0	0	[illegible]
TOTAL	162	3	1	0	0	1	0	0	157	0	0	2	0	[illegible]

	Total Fathers	Failed Cultures	Secondary Constriction #1 Uncoiled #1 (A) Code "1"	Code "2"	Code "3"	Code "4"	Code "5"	Code "6"	Code "7"	Secondary Constricti Code "1"	Code "2"	Code "3"	Code "4"	Co "
MATCHED PAIRS														
Exposed	55	0	0	1	0	0	0	1	53	0	0	1	0	
Unexposed	55	1	0	0	0	0	0	0	54	0	0	0	0	
Near Exposure	7	0	0	0	0	0	0	0	7	0	0	0	0	
Unexposed	7	0	0	0	0	0	0	0	7	0	0	0	0	
UNMATCHED														
Exposed	14	0	0	0	0	0	0	0	14	0	0	0	0	
Near Exposure	12	0	0	0	0	0	0	0	12	0	0	0	0	
Unexposed	12	2	0	0	0	0	0	0	10	0	0	0	0	
TOTAL	162	3	0	1	0	0	0	1	157	0	0	1	0	

⊙Category A - Cytological abnormality or variation: including long #2, long short arm G, second

Code Numbers

1 = yes, in all successful cultures (including just 1 successful done) in all cells
2 = yes, in all successful cultures (including just 1 successful done) presumed to be in a
abnormalities e.g. prominent satellite) or not counted just noted
3 = yes, in all successful cultures (including just 1 successful done) in >1 cell, not all
4 = yes, in all successful cultures (including just 1 successful done) in 1 cell only
5 = yes, in 1 or more successful cultures, but not in all cultures, found in >1 cell of on
6 = yes, in 1 or more successful cultures, but not in all cultures, found in only 1 cell o
7 = no, in all successful cultures

OSOMAL VARIANTS IN CATEGORY "A" BY APPEARANCE IN BLOOD CULTURES

ng #2's (A)					Fragile #16 (A)							Long Short Arm G(A)						
de "3"	Code "4"	Code "5"	Code "6"	Code "7"	Code "1"	Code "2"	Code "3"	Code "4"	Code "5"	Code "6"	Code "7"	Code "1"	Code "2"	Code "3"	Code "4"	Code "5"	Code "6"	Code "7"
0	1	0	0	53	0	0	0	0	0	0	55	0	1	0	0	0	0	54
0	0	0	0	54	0	0	1	0	0	0	53	0	0	0	0	0	0	54
0	0	0	0	7	0	0	0	0	0	0	7	0	0	0	0	0	0	7
0	0	0	0	7	0	0	0	0	0	0	7	0	0	0	0	0	0	7
0	0	0	0	14	0	0	1	0	0	0	13	0	0	0	0	0	0	14
0	0	0	0	12	0	0	0	0	0	0	12	0	0	0	0	0	0	12
0	0	0	0	10	0	0	0	0	0	0	10	0	0	0	0	0	0	10
0	1	0	0	157	0	0	2	0	0	0	157	0	1	0	0	0	0	158

Constriction #1 iled #1 (A)					Secondary Constriction #9(A)							Prominent D Satellite (A)						
e "	Code "4"	Code "5"	Code "6"	Code "7"	Code "1"	Code "2"	Code "3"	Code "4"	Code "5"	Code "6"	Code "7"	Code "1"	Code "2"	Code "3"	Code "4"	Code "5"	Code "6"	Code "7"
	0	0	1	53	0	0	1	0	0	0	54	0	1	0	0	0	0	54
	0	0	0	54	0	0	0	0	0	0	54	0	1	0	0	0	0	53
	0	0	0	7	0	0	0	0	0	0	7	0	0	0	0	0	0	7
	0	0	0	7	0	0	0	0	0	0	7	0	0	0	0	0	0	7
	0	0	0	14	0	0	0	0	0	0	14	0	0	0	0	0	0	14
	0	0	0	12	0	0	0	0	0	0	12	0	0	0	0	0	0	12
	0	0	0	10	0	0	0	0	0	0	10	0	0	0	0	0	0	10
	0	0	1	157	0	0	1	0	0	0	158	0	2	0	0	0	0	157

: including long #2, long short arm G, secondary constriction #1, fragile #16, uncoiled #1, etc.

Code Numbers

ng just 1 successful done) in <u>all</u> cells
ng just 1 successful done) presumed to be in all cells but not always visible (as in A
or not counted just noted
ng just 1 successful done) in >1 cell, not all
ng just 1 successful done) in 1 cell only
ut not in all cultures, found in >1 cell of one culture, or >1 cell of >1 culture
ut not in all cultures, found in only 1 cell of any culture

TABLE CS4

SUMMARY OF CHROMOSOMAL ABNORMALITIES IN CATEGORY "B" ⊙ BY APP

(excluding Endoreduplication)

	Total Fathers	Failed Cultures	Strands Between Chromosomes (B)							Quadrira		
			Code "1"	Code "2"	Code "3"	Code "4"	Code "5"	Code "6"	Code "7"	Code "1"	Code "2"	Code "3"
MATCHED PAIRS												
Exposed	55	0	0	1	0	0	0	0	54	0	0	0
Unexposed	55	1	0	0	0	0	0	0	54	0	0	0
Near Exposure	7	0	0	0	0	0	0	0	7	0	0	0
Unexposed	7	0	0	0	0	0	0	0	7	0	0	0
UNMATCHED												
Exposed	14	0	0	0	0	0	0	0	14	0	0	0
Near Exposure	12	0	0	0	0	0	0	0	12	0	0	0
Unexposed	12	2	0	0	0	0	0	0	10	0	0	0
TOTAL	162	3	0	1	0	0	0	0	158	0	0	0

	Total Fathers	Failed Cultures	Fragmented (B)							Double Chr		
			Code "1"	Code "2"	Code "3"	Code "4"	Code "5"	Code "6"	Code "7"	Code "1"	Code "2"	Code "3"
MATCHED PAIRS												
Exposed	55	0	0	0	2	3	0	0	50	0	0	2
Unexposed	55	1	0	0	0	11	0	1	42	0	0	1
Near Exposure	7	0	0	0	0	0	0	0	7	0	0	0
Unexposed	7	0	0	0	0	0	0	0	7	0	0	0
UNMATCHED												
Exposed	14	0	0	0	1	5	0	1	7	0	0	0
Near Exposure	12	0	0	0	0	2	0	0	10	0	0	0
Unexposed	12	2	0	0	0	1	0	0	9	0	0	0
TOTAL	162	3	0	0	3	22	0	2	132	0	0	3

⊙ Category B - Abnormality that may be due to a mutagenic agent: including quadriradial, breaks, etc.

Code Numbers

1 = yes, in all successful cultures (including just 1 successful done) in
2 = yes, in all successful cultures (including just 1 successful done) pre abnormalities e.g. prominent satellite or not counted just noted
3 = yes, in all successful cultures (including just 1 successful done) in
4 = yes, in all successful cultures (including just 1 successful done) in
5 = yes, in 1 or more successful cultures, but not in all cultures, found
6 = yes, in 1 or more successful cultures, but not in all cultures, found
7 = no, in all successful cultures

BIBLIOGRAPHY

BNORMALITIES IN CATEGORY "B" BY APPEARANCE IN BLOOD CULTURES

(excluding Endoreduplication)

Chromosomes (B)			Quadriradials (B)							Dicentrics (B)						
Code "5"	Code "6"	Code "7"	Code "1"	Code "2"	Code "3"	Code "4"	Code "5"	Code "6"	Code "7"	Code "1"	Code "2"	Code "3"	Code "4"	Code "5"	Code "6"	Code "7"
0	0	54	0	0	0	0	0	1	54	0	0	0	1	0	1	53
0	0	54	0	0	0	1	0	0	53	0	0	0	2	0	0	52
0	0	7	0	0	0	0	0	0	7	0	0	0	0	0	0	7
0	0	7	0	0	0	0	0	0	7	0	0	0	0	0	0	7
0	0	14	0	0	0	0	0	0	14	0	0	0	0	0	1	13
0	0	12	0	0	0	0	0	0	12	0	0	0	0	0	0	12
0	0	10	0	0	0	0	0	0	10	0	0	0	0	0	0	10
0	0	158	0	0	0	1	0	1	157	0	0	0	3	0	2	154

(B)			Double Chromatid Breaks (B)							Isochromatid Breaks (B)						
Code "5"	Code "6"	Code "7"	Code "1"	Code "2"	Code "3"	Code "4"	Code "5"	Code "6"	Code "7"	Code "1"	Code "2"	Code "3"	Code "4"	Code "5"	Code "6"	Code "7"
0	0	50	0	0	2	5	0	1	47	0	0	0	0	0	0	55
0	1	42	0	0	1	3	0	0	50	0	0	0	0	0	0	54
0	0	7	0	0	0	1	0	0	6	0	0	0	1	0	0	6
0	0	7	0	0	0	1	0	0	6	0	0	0	0	0	0	7
0	1	7	0	0	0	0	0	0	14	0	0	0	0	0	0	14
0	0	10	0	0	0	3	0	0	9	0	0	0	0	0	0	12
0	0	9	0	0	0	0	0	0	10	0	0	0	0	0	0	10
0	2	132	0	0	3	13	0	1	142	0	0	0	1	0	0	158

agenic agent: including quadriradial, endoreduplication, fragmented, dicentric, double chromatid breaks, etc.

Code Numbers

(including just 1 successful done) in all cells
(including just 1 successful done) presumed to be in all cells but not always visible (as in A
llite or not counted just noted
(including just 1 successful done) in >1 cell, not all
(including just 1 successful done) in 1 cell only
ures, but not in all cultures, found in >1 cell of one culture, or >1 cell of >1 culture
ures, but not in all cultures, found in only 1 cell of any culture

TABLE CS-5

ENDOREDUPLICATION (B CATEGORY VARIANT)

	Total Fathers	Failures	% Tot.	Code "1"	% Suc.	Code "2"	% Suc.	Code "3"	% Suc.	Code "4"	% Suc.	Code "5"
MATCHED PAIRS												
Exposed	55	0	0	0	0	0	0	1	1.8	6	10.9	0
Unexposed	55	1	1.8	0	0	0	0	1	1.9	9	16.7	0
Near Exposed	7	0	0	0	0	0	0	0	0	0	0	0
Unexposed	7	0	0	0	0	0	0	0	0	1	14.3	0
UNMATCHED												
Exposed	14	0	0	0	0	0	0	0	0	1	7.1	0
Near Exposed	12	0	0	0	0	0	0	0	0	1	8.3	0
Unexposed	12	2	16.7	0	0	0	0	0	0	1	10.0	0
TOTAL	162	3	1.9	0	0	0	0	2	1.3	19	11.9	0

Code Numbers

1 = yes, in all successful cultures (including just 1 successful done) in all cells
2 = yes, in all successful cultures (including just 1 successful done) presumed to be in all c
abnormalities e.g. prominent satellite) or not counted just noted
3 = yes, in all successful cultures (including just 1 successful done) in >1 cell, not all
4 = yes, in all successful cultures (including just 1 successful done) in 1 cell only
5 = yes, in 1 or more successful cultures, but not in all cultures, found in >1 cell of one cu
6 = yes, in 1 or more successful cultures, but not in all cultures, found in only 1 cell of ar
7 = no, in all successful cultures

ENDOREDUPLICATION (B CATEGORY VARIANT)

Code "2"	% Suc.	Code "3"	% Suc.	Code "4"	% Suc.	Code "5"	% Suc.	Code "6"	% Suc.	Code "7"	% Suc.	
0	0	1	1.8	6	10.9	0	0	1	1.8	47	85.5	N = 55
0	0	1	1.9	9	16.7	0	0	0	0	44	81.5	N = 54
0	0	0	0	0	0	0	0	0	0	7	100.0	N = 7
0	0	0	0	1	14.3	0	0	0	0	6	85.7	N = 7
0	0	0	0	1	7.1	0	0	0	0	13	92.9	N = 14
0	0	0	0	1	8.3	0	0	0	0	11	91.7	N = 12
0	0	0	0	1	10.0	0	0	0	0	9	90.0	N = 10
0	0	2	1.3	19	11.9	0	0	1	0.6	137	86.2	N =159

Code Numbers

just 1 successful done) in <u>all</u> cells
just 1 successful done) presumed to be in all cells but not always visible (as in A
not counted just noted
just 1 successful done) in >1 cell, not all
just 1 successful done) in 1 cell only
not in all cultures, found in >1 cell of one culture, or >1 cell of >1 culture
not in all cultures, found in only 1 cell of any culture

TABLE CS-6

SUMMARY OF CHROMOSOMAL ABNORMALITIES IN CATEGORY "C" BY APPEARANCE

	Total Fathers	Failed Cultures	Gaps (C)						
			Code "1"	Code "2"	Code "3"	Code "4"	Code "5"	Code "6"	Code "7"
MATCHED PAIRS									
Exposed	55	0	0	0	2	14	0	1	38
Unexposed	55	1	0	0	3	6	0	1	44
Near Exposure	7	0	0	0	1	3	0	0	3
Unexposed	7	0	0	0	0	0	0	0	7
UNMATCHED									
Exposed	14	0	0	0	0	1	0	0	13
Near Exposure	12	0	0	0	0	2	0	0	10
Unexposed	12	2	0	0	0	1	0	0	9
TOTAL	162	3	0	0	6	27	0	2	124

Category C - "Abnormality" that may be due to mechanical or technical error: including gaps

Code Numbers

1 = yes, in all successful cultures (including just 1 successful done) in all cells
2 = yes, in all successful cultures (including just 1 successful done) presumed to be in all
abnormalities e.g. prominent satellite) or not counted just noted
3 = yes, in all successful cultures (including just 1 successful done) in >1 cell, not all
4 = yes, in all successful cultures (including just 1 successful done) in 1 cell only
5 = yes, in 1 or more successful cultures, but not in all cultures, found in >1 cell of one c
6 = yes, in 1 or more successful cultures, but not in all cultures, found in only 1 cell of a
7 = no, in all successful cultures

RMALITIES IN CATEGORY "C" BY APPEARANCE IN BLOOD CULTURES

Gaps (C)							Single Chromatid Breaks (C)						
Code "1"	Code "2"	Code "3"	Code "4"	Code "5"	Code "6"	Code "7"	Code "1"	Code "2"	Code "3"	Code "4"	Code "5"	Code "6"	Code "7"
0	0	2	14	0	1	38	0	0	2	7	0	0	46
0	0	3	6	0	1	44	0	0	1	5	0	1	47
0	0	1	3	0	0	3	0	0	0	1	0	0	6
0	0	0	0	0	0	7	0	0	0	0	0	0	7
0	0	0	1	0	0	13	0	0	0	2	0	0	12
0	0	0	2	0	0	10	0	0	0	2	0	0	10
0	0	0	1	0	0	9	0	0	0	2	0	0	8
0	0	6	27	0	2	124	0	0	3	19	0	1	136

ical or technical error: including gaps or single chromatid breaks

Code Numbers

1 successful done) in all cells
1 successful done) presumed to be in all cells but not always visible (as in A
counted just noted
1 successful done) in >1 cell, not all
1 successful done) in 1 cell only
in all cultures, found in >1 cell of one culture, or >1 cell of >1 culture
in all cultures, found in only 1 cell of any culture

TABLE CS-7

NUMBER OF ABNORMAL CELLS BY EXPOSURE-MATCHING STATUS OF F

	Total Fathers	None Incl. Failures		Number of Abnormal Ce							
				1		2		3		4	
		No.	%	No.	%	No.	%	No.	%	No.	%
MATCHED PAIRS											
Exposed	55	22	40.0	14	25.5	8	14.5	2	3.6	2	3.6
Unexposed	55	24	43.6	13	23.6	7	12.7	4	7.3	3	5.5
Near Exposed	7	3	42.9	1	14.3	2	28.6	1	14.3	0	0
Unexposed	7	5	71.4	2	28.6	0	0	0	0	0	0
UNMATCHED											
Exposed	14	5	35.7	4	28.6	4	28.6	0	0	0	0
Near Exposed	12	6	50.0	4	33.3	0	0	2	16.7	0	0
Unexposed	12	8	66.7	3	25.0	1	8.3	0	0	0	0
TOTAL	162	72	44.4	41	25.3	23	14.2	9	5.6	5	3.1

F ABNORMAL CELLS BY EXPOSURE-MATCHING STATUS OF FATHERS

	Number of Abnormal Cells													
	2		3		4		5		6		7+		Abn. in All Cells	
%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
.5	8	14.5	2	3.6	2	3.6	1	1.8	0	0	1	1.8	5	9.1
.6	7	12.7	4	7.3	3	5.5	0	0	0	0	3	5.5	1	1.8
.3	2	28.6	1	14.3	0	0	0	0	0	0	0	0	0	0
.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0
.6	4	28.6	0	0	0	0	1	7.1	0	0	0	0	0	0
.3	0	0	2	16.7	0	0	0	0	0	0	0	0	0	0
.0	1	8.3	0	0	0	0	0	0	0	0	0	0	0	0
3	23	14.2	9	5.6	5	3.1	2	1.2	0	0	4	2.5	6	3.7

100.0	0	24	
78.2	12	15	34.9
66.7	5	4	40.0
60.0	2	3	0
100.0	0	0	0
0	0	0	0
75.6	19	22	37.3
98.2	1		
76.4	13	20	47.6
73.3	4	3	27.3
66.7	1	1	50.0
0	1	0	0
100.0	0	0	100.0
74.7	19	25	44.6
100.0	0		
85.7	1	3	50.0
100.0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
87.5	1	3	42.9

% Suc.	C	% Suc.	All B	% Suc.
11.6	6	14.0	20	46.5
0	5	50.0	0	0
0	0	0	0	0
66.7	1	33.3	2	66.7
0	0	0	0	0
11.9	12	20.3	23	40.0
11.9	5	11.9	14	33.3
9.1	1	9.1	8	72.7
0	0	0	1	50.0
0	0	0	0	0
0	0	0	0	0
10.7	6	10.7	23	41.1
16.7	2	33.3	1	16.7
0	1	100.0	0	1
0	0	0	0	0
0	0	0	0	0
0	0	0	0	0
14.3	3	42.9	1	14.3

TABLE CS-8B

DISTRIBUTION OF CHROMOSOME RESULTS BY SPECIMEN AND PATE
Unmatched Fathers

	Total	Successful Cultures	% Total	Failures	D	% Suc.	A	% Suc.	AB	% Suc.	AC	% Suc.	AB
UNMATCHED													
Exposed													
Total Subjects	14	14	100.0	0									
1st Specimen	14	10	71.4	4	2	20.0	1	10.0	0	0	0	0	0
2nd Specimen	6	3	50.0	3	2	66.7	0	0	1	33.3	0	0	0
3rd Specimen	3	3	100.0	0	1	33.3	0	0	0	0	0	0	0
4th Specimen	0	0	0	0	0	0	0	0	0	0	0	0	0
5th Specimen	0	0	0	0	0	0	0	0	0	0	0	0	0
Total Specimens	23	16	69.6	7	5	31.3	1	6.3	1	6.3	0	0	0
Near Exposed													
Total Subjects	12	12	100.0	0									
1st Specimen	12	11	91.7	1	6	0	0	0	0	0	0	0	0
2nd Specimen	1	1	100.0	0	0	0	0	0	0	0	0	0	0
3rd Specimen	0	0	0	0	0	0	0	0	0	0	0	0	0
4th Specimen	0	0	0	0	0	0	0	0	0	0	0	0	0
5th Specimen	0	0	0	0	0	0	0	0	0	0	0	0	0
Total Specimens	13	12	92.3	1	6	50.0	0	0	0	0	0	0	0
Unexposed													
Total Subjects	12	10	83.3	2									
1st Specimen	12	8	66.7	4	5	27.8	0	0	0	0	0	0	0
2nd Specimen	2	2	100.0	0	1	50.0	0	0	0	0	0	0	0
3rd Specimen	0	0	0	0	0	0	0	0	0	0	0	0	0
4th Specimen	0	0	0	0	0	0	0	0	0	0	0	0	0
5th Specimen	0	0	0	0	0	0	0	0	0	0	0	0	0
Total Specimens	14	10	71.4	4	6	60.0	0	0	0	0	0	0	0

X Categories D, A, B, C, AB, AC, BC and ABC are mutually exclusive (as in T
Categories "all B", "all A", "all C" are respectively synonymous with "any
and are not mutually exclusive, i.e., cultures showing multiple defects a
example, cultures with both A and B defects would be counted in "any A" a

S BY SPECIMEN AND PATERNAL EXPOSURE-MATCHING STATUS AND CATEGORY (x)
Unmatched Fathers

% Suc.	AC	% Suc.	ABC	% Suc.	B	% Suc.	BC	% Suc.	C	% Suc.	All B	% Suc.	All A	% Suc.	All C	% Suc.
0	0	0	0	0	5	50.0	1	10.0	1	10.0	6	60.0	1	10.0	2	20.0
33.3	0	0	0	0	0	0	0	0	0	0	1	33.3	0	0	0	0
0	0	0	0	0	1	33.3	0	0	1	33.3	1	33.3	0	0	1	33.3
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6.3	0	0	0	0	6	37.5	1	6.3	2	12.5	8	50.0	2	12.5	3	18.8
0	0	0	0	0	1	9.1	2	18.2	2	18.2	3	27.3	0	0	4	36.4
0	0	0	0	0	1	100.0	0	0	0	0	1	100.0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	2	16.7	2	16.7	2	16.7	4	33.3	0	0	4	33.3
0	0	0	0	0	1	12.5	0	0	2	25.0	1	0	0	0	2	25.0
0	0	0	0	0	1	50.0	0	0	0	0	1	50.0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	2	20.0	0	0	2	20.0	2	20.0	0	0	2	20.0

tually exclusive (as in Table CS-2A).
tively synonymous with "any B", "any A", and "any C" respectively of Table CS-2B
howing multiple defects are counted in any and all categories applicable, for
d be counted in "any A" and again in "any B".

FIGURE 2 Some Types of Chromosome Aberrancy Observed

a.) Secondary Constriction; b.) Quadriradial; c.) Dicentric; d.) Fragment; e.) Isochromatid Break; f.) Gap

FIGURE 3 Endoreduplication

abnormalities e.g. prominent satellite or not counted just noted
3 = yes, in all successful cultures (including just 1 successful done) in >
4 = yes, in all successful cultures (including just 1 successful done) in 1
5 = yes, in 1 or more successful cultures, but not in all cultures, found i
6 = yes, in 1 or more successful cultures, but not in all cultures, found i
7 = no, in all successful cultures

BIBLIOGRAPHY

1. Cohen, B. H., Lilienfeld, A. M., and Sigler, A. T. 1963. Some epidemiological aspects of mongolism: a review. Am. J. Public Health 53:224-236.

2. Sigler, A. T., Lilienfeld, A. M., Cohen, B. H., and Westlake, J. E. 1965. Parental age in Down's syndrome (mongolism). J. Ped. 67: 631-642.

3. ______________________________. 1965. Radiation exposure in parents of children with mongolism (Down's syndrome). Bull. Johns Hopkins Hosp. 117:374-399.

4. Sigler, A. T., Cohen, B. H., Lilienfeld, A. M., Westlake, J. E., and Hetznecker, W. H. 1967. Reproductive and marital experience of parents of children with Down's syndrome (mongolism). J. Ped. 70: 608-614.

5. Cohen, B. H. and Lilienfeld, A. M. 1970. The epidemiological study of mongolism in Baltimore. Ann. N.Y. Acad. Sci. 171:320-327.

6. Lejeune, J., Gautier, M., and Turpin, R. 1959. Etudes des chromosomes somatique de neuf enfants mongoliens. C. R. Acad. Sci. 248: 1721-1722.

7. Lilienfeld, A. M. and Benesch, C. H. 1969. Epidemiology of Mongolism. The Johns Hopkins Press, Baltimore.

8. Penrose, L. S. and Smith, G. F. 1966. Down's Anomaly. Little, Brown and Co., Boston.

9. Apgar, Virginia (ed.). 1970. Down's Syndrome (Mongolism). Ann. N.Y. Acad. Sci. 171 (2):303-688.

10. Carter, C. and MacCarthy, D. 1951. Incidence of mongolism and its diagnosis in the newborn. Brit. J. Soc. Med. 5:83-90.

11. Oster, J. 1953. Mongolism: A Clinicogenealogical Investigation Comprising 526 Mongols Living on Seeland and Neighboring Islands in Denmark. Danish Science Press, Copenhagen.

12. __________. 1956. The causes of mongolism. Dan. Med. Bull. 3:158-164.

13. Collmann, R. D. and Stoller, A. 1962. A survey of mongoloid births in Victoria, Australia, 1942-1957. Am. J. Public Health 52:813-829.

14. Matsunaga, E. 1963. Down's syndrome in Japan. Nat. Inst. Genet. Ann. Rep. 14:128-130.

15. Davidenkova, E. F., Shtil'bans, I. I., Godinova, A. M., Savel'eva-Vasil'eva, E. A., and Berlinskaya, D. K. 1964. Role of maternal pathology in Down's disease. Fed. Proc. Trans., Suppl. 23:873-875.

16. Renwick, D. H., Miller, J. R., and Paterson, D. 1964. Estimates of incidence and prevalence of mongolism and of congenital heart disease in British Columbia. Can. Med. Assoc. J. 91:365-371.

llite or not counted just noted
(including just 1 successful done) in >1 cell, not all
(including just 1 successful done) in 1 cell only
tures, but not in all cultures, found in >1 cell of one culture, or >1 cell of >1 culture
tures, but not in all cultures, found in only 1 cell of any culture

17. Chitham, R. G. and MacGiver, E. 1965. A cytogenetic and statistical survey of 105 cases of mongolism. Ann. Hum. Genet. 28:309-315.

18. Tonomura, A., Oishi, H., Matsunaga, E., and Kurita, T. 1966. Down's syndrome: a cytogenetic and statistical survey of 127 Japanese patients. Jap. J. Hum. Genet. 11:1-16.

19. Akesson, H. O. and Forssman, H. 1966. A study of maternal age in Down's syndrome. Ann. Hum. Genet. 29:271-276.

20. Stevenson, A. C., Johnston, H. A., Stewart, M. I., and Golding, D. R. 1966. Congenital malformations: a report of a study of series of consecutive births in 24 centers. Bull. W.H.O., Suppl. 34:9-127.

21. Stark, C. R. and Mantel, N. 1966. Effects of maternal age and birth order on the risk of mongolism and leukemia. J. Nat. Cancer Inst. 37:687-698.

22. Halevi, H. S. 1967. Congenital malformations in Israel. Brit. J. Prev. Soc. Med. 21:66-77.

23. Burch, P. R. J. 1969. Down's syndrome and maternal age. Nature 221: 173-175.

24. Stene, J. 1970. Detection of higher recurrence risk for age-dependent chromosome abnormalities with an application to trisomy G_1 (Down's syndrome). Hum. Hered. 20: 112-122.

25. Morris, R. 1971. Down's syndrome in New Zealand. New Zealand Med. J. 73:195-198.

26. Mikkelsen, M. and Stene, J. 1972. The effect of maternal age on the incidence of Down's syndrome. Humangenetik 16:141-146.

27. Matsunaga, E. and Tonomura, A. 1972. Parental age and birth weight in translocation Down's syndrome. Ann. Hum. Genet. 36:209-219.

28. Richards, B. W. 1973. Mongols and their mothers. Brit. J. Psychiat. 122:1-14.

29. Moran, P. A. P. 1974. Are there two maternal age groups in Down's syndrome? Brit. J. Psychiat. 124:453-455.

30. Renkonen, K. O. and Donner, M. 1964. Mongoloids, their mothers and sibships. Ann. Med. Exp. Fenn. 42:139-144.

31. Rundle, A., Atkin, J. and Sudell, B. 1974. Effects of parental age on some phenotype frequencies in Down's syndrome. Humangenetik. 23: 137-148.

32. Spencer, D. A. 1971. Down's syndrome: sex difference in relation to maternal age. Lancet 1:1356.

33. Largey, G. P. and Largey, K. A. 1971. Down's syndrome: sex difference in relation to maternal age. Lancet 1:1242.

34. Fedrick, J. 1971. Down's syndrome: sex difference in relation to maternal age. Lancet 2:45.

35. Perry, T. B. 1971. Down's syndrome: sex difference in relation to maternal age. Lancet 2:263-264.

36. Collman, R. D. and Stoller, A. 1969. Shift of childbirth to younger mothers and its effects on the incidence of mongolism in Victoria, Australia, 1939-1964. J. Ment. Defic. Res. 13:13-19.

37. Zellweger, H. and Simpson, J. 1973. Is routine prenatal karyotyping indicated in pregnancies of very young women? J. Pediatr. 82:675-676.

38. Kucheria, K. 1974. Down's syndrome in children born to young mothers. J. Indian Med. Assoc. 63:191-192.

39. Jones, D. C. and Lowry, R. B. 1975. Falling maternal age and incidence of Down's syndrome. Lancet 1:753-754.

40. Shiono, H., Kadowaki, J., and Nakao, T. 1975. Maternal age and Down's syndrome: the shift of affected infants to younger mothers in Hokkaido. Clin. Pediatr. 14:241-244.

41. Jenkins, R. L. 1933. Etiology of mongolism. Amer. J. Dis. Child. 45:506-519.

42. Penrose, L. S. 1933. The relative effects of paternal and maternal age in mongolism. J. Genet. 27:219-224.

43. ______________. 1962. Paternal age in mongolism. Lancet 1:1101.

44. Greenberg, R. C. 1963. Two factors influencing the births of mongols to younger mothers. Med. Off. 109:62-64.

45. Milham, S., Jr. and Gittelsohn, A. M. 1965. Parental age and malformations. Hum. Biol. 37:13-22.

46. Matsunaga, E. 1967b. Parental age, live-birth order and pregnancy-free interval in Down's syndrome in Japan. Ciba Foundation Study Group No. 25, Mongolism, pp. 6-22. Little, Brown & Co., Boston.

47. ______________. 1967a. General discussion. Ciba Foundation Study Group No. 25, Mongolism, pp. 88-95. Little, Brown & Co., Boston.

48. German, J. 1968. Mongolism, delayed fertilization and human sexual behavior. Nature 217:516-518.

49. Penrose, L. S. and Berg, J. M. 1968. Mongolism and duration of marriage. Nature 218:300.

50. Cannings, C. and Cannings, M. R. 1968. Mongolism, delayed fertilization, and human sexual behavior. Nature 218:481.

51. Matsunaga, E. and Maruyama, T. 1969. Human sexual behavior, delayed fertilization and Down's syndrome. Nature 221:642-644.

52. Penrose, L. S. 1954. Observations on the aetiology of mongolism. Lancet 2:505.

53. ______________. 1964. Genetical aspects of mental deficiency. Proc. International Copenhagen Congress on the Scientific Study of Mental Retardation (2nd Conf.) 1:165.

54. Forssman, H. and Akesson, H. O. 1967. Consanguineous marriages and mongolism. Ciba Foundation Study Group No. 25, Mongolism, pp. 23-34. Little, Brown & Co., Boston.

55. Stoller, A. and Collman, R. D. 1969. Grandmaternal age at birth of mothers of children with Down's syndrome (mongolism). J. Ment. Defic. Res. 13: 201-5.

56. Papp, Z., Csecsel, K., Skapinyecz, J. and Dolhay, B. 1974. Paternal normal/trisomy 21 mosaicism as an indication for amniocentesis. Clinical Genetics 6:192-194.

57. Smith, A. and McKeown, T. 1955. Pre-natal growth of mongoloid defectives. A.M.A. Arch. Dis. Child 30:257.

58. Smith, A. and Record, R. G. 1955. Fertility and reproductive history of mothers of mongoloid defectives. Brit. J. Prev. Soc. Med. 9:51-55.

59. Ingalls, T. H., Babbott, J., and Philbrook, R. 1957. The mothers of mongoloid babies: a retrospective appraisal of their health during pregnancy. Am. J. Obstet. Gynecol. 74:572-581.

60. Lunn, J. E. 1959. A survey of mongol children in Glasgow. Scot. Med. J. 4:368-371.

61. Coppen, A. and Cowie, V. 1960. Maternal health and mongolism. Brit. Med. J. 1:1843-1847.

62. Berg, J. M. and Kirman, B. H. 1961. Risk of dual occurrence of mongolism in sibships. Arch. Dis. Child. 36:645-648.

63. Carter, C. O. and Evans, K. A. 1961. Risk of parents who have had one child with Down's syndrome having another child similarly affected. Lancet 2:785-788.

64. Rundle, A., Coppen, A. and Cowie, V. 1961. Steroid excretion in mothers of mongols. Lancet 2:846-848.

65. Cowie, V. and Slater, E. 1963. Maternal age and miscarriage in mothers of mongols. Acta. Genet. 13:77-83.

66. Buck, C., Valentine, G. H. and Hamilton, K. 1966. Reproductive performance of mothers of mongols. Am. J. Ment. Def. 70:886-894.

67. Cowie, V. and Slater, E. 1968. The fertility of mothers of mongols. J. Ment. Defic. Res. 12:196-208.

68. Berg, J. M. and Bavin, J. T. R. 1969. Mongolism and maternal menarche. J. Med. Genet. 6:135-136.

69. Marmol, J. G., Scriggins, A. L., and Vollman, R. F. 1969. Mothers of mongoloid infants in the collaborative project. Am. J. Obstet. Gynecol. 104:533-543.

70. Burch, P. R. 1969. Down's syndrome and maternal age. Nature 221:173.

71. James, W. H. 1970. Curve fitting, maternal age, and mongolism. Hum. Hered. 20:417-419.

72. Kaplan, A. R. and Zsako, S. 1970. Biological variables associated with mothers of children affected with G_1-trisomy syndrome (Down's syndrome). Am. J. Ment. Defic. 74:745-755.

73. Ingalls, T. H. 1972. Maternal health and mongolism. Lancet 2:213-315.

74. Bech, K. and Tygstrup, I. 1972. Down's syndrome and oestriol excretion in late pregnancy. Lancet 2:1261.

75. Jorgensen, P. I. and Trolle, D. 1972. Low urinary oestriol excretion during pregnancy in women giving birth to infants with Down's syndrome. Lancet 2:782-784.

76. McDonald, A. D. 1972. Thyroid disease and other maternal factors in mongolism. Can Med. Assoc. J. 106:1085-1089.

77. Juberg, R. C., Goshen, C. R. and Sholte, F. G. 1973. Socioeconomic and reproductive characteristics of parents of patients with the G_1-trisomy syndrome. Soc. Bio. 20:404-415.

78. Ek, J. I. 1959. Thyroid function in mothers of mongoloid infants. Acta. Paed. 48:33-42.

79. Fialkow, P. J., Hecht, F., Bryant, J. and Motulsky, A. 1965. Familial predisposition to chromosomal aberrations. Clin. Res. 13:124.

80. Fialkow, P. J., Uchida, I. A., Hecht, F. and Motulsky, A. G. 1965. Increased frequency of autoantibodies in mothers of patients with Down's syndrome. Lancet 2:868-870.

81. Burgio, G. R., Severi, F., Rossoni, R. and Vaccaro, R. 1966. Autoantibodies in Down's syndrome. Lancet 1:497-498.

82. Fialkow, P. J. 1966. Autoimmunity and chromosomal aberrations. Am. J. Hum. Genet. 18:93-108.

83. ____________. 1967. Thyroid antibodies, Down's syndrome, and maternal age. Nature 214:1253-1254.

84. Dallaire, L., Kingsmill-Flynn, D., and Leboeuf, G. 1969. Autoimmunity and chromosomal aberrations: serological studies in mothers with Down's syndrome. Can. Med. Assoc. J. 100:1-4.

85. Vaccaro, R., Rossoni, R. and Alestra, P. 1969. Further research into the incidence of autoimmune disorders in patients with Down's syndrome and their parents. Minerva Ped. 2:1175-1183.

86. Schuler, D., Koos, R., Siegler, J. and Horvath, L. 1970. Thyroid autoantibodies and satellite associations in Down's syndrome. Hum. Hered. 20:13-18.

87. Fialkow, P. J. 1970. Thyroid autoimmunity and Down's syndrome. Ann. N. Y. Acad. Sci. 171:500-511.

88. Vanhaelst, L., Hayez, F., Bonnyns, M. and Bastenie, P. A. 1970. Thyroid autoimmune disease and thyroid function in families of subjects with Down's syndrome. J. Clin. Endocrinol. Metab. 30:792-797.

89. Fialkow, P. J., Thuline, H. C., Hecht, F. and Bryant, J. 1971. Familial predisposition to thyroid disease in Down's syndrome: controlled immunoclinical studies. Am. J Hum. Genet. 23:67-86.

90. Fialkow, P. J., Blumberg, B. S., London, W. T., Sutnick, A. I. and Thuline, H. C. 1971. Thyroid antibodies and Australia antigen in Down's syndrome. J. Ment. Defic. Res. 15:177-180.

91. Vallotton, M. B. and Forbes, A. P. 1969. Premature menopause in autoimmune diseases. Lancet 1:156.

92. Milunsky, A. 1970. Glucose intolerance in the parents of children with Down's syndrome. Am. J. Ment. Defic. 74:475-478.

93. Comfort, A. 1972. Accelerated aging in young mothers of children with Down's syndrome. Lancet 2:537.

94. Thompson, M. K. 1972. Accelerated aging in young mothers of children with Down's syndrome. Lancet 2:602-603.

95. Emanuel, I., Sever, L. E., Milham, S. and Thuline, H. C. 1972. Accelerated aging in young mothers of children with Down's syndrome. Lancet 2: 361-363.

96. Fialkow, P. J., Martin, G. M. and Sprague, C. A. 1973. Replicative life span of cultured skin fibroblasts from young mothers of subjects with Down's syndrome: failure to detect accelerated aging. Am. J. Hum. Genet. 25:317-322.

97. Rapaport, I. 1963. Mongolian oligophrenia and dental caries. Rev. Stomat. 64:207-218.

98. Greenberg, R. C. 1964. Some factors in the epidemiology of mongolism. Proc. International Copenhagen Congress on the Scientific Study of Mental Retardation 1:200-202.

99. Needleman, H. L., Pueschel, S. M. and Rothman, K. J. 1974. Fluoridation and the occurrence of Down's syndrome. N. Engl. J. Med. 291: 821-823.

100. Pleydell, M. J. 1957. Mongolism and other congenital abnormalities: an epidemiological study in Northamptonshire. Lancet 1:1314-1319.

101. Heinrichs, E. H., Allen, S. W. and Nelson, P. S. 1963. Simultaneous 18-trisomy and 21-trisomy cluster. Lancet 2:468.

102. Stoller, A. and Collmann, R. D. 1965a. Incidence of infective hepatitis followed by Down's syndrome nine months later. Lancet 2:1221-1223.

103. ______________________________. 1965b. Patterns of occurrence of births in Victoria, Australia, producing Down's syndrome (mongolism) and congenital anomalies of the central nervous system: a 21-year prospective and retrospective survey. Med. J. Aust. 1:1-4.

104. ______________________________. 1965c. Virus aetiology for Down's syndrome (mongolism). Nature 208:903-904.

105. ______________________________. 1966. Area relationship between incidences of infectious hepatitis and of the births of children with Down's syndrome nine months later. J. Ment. Defic. Res. 10:84-88.

106. Robinson, A. and Puck, T. T. Infective hepatitis and Down's syndrome. Lancet 1:313-314.

107. Stark, C. R. and Fraumeni, J. E. 1966. Viral hepatitis and Down's syndrome. Lancet 1:1036.

108. Leck, I. 1966. Incidence and epidemicity of Down's syndrome. Lancet 2:457-460.

109. Fraumeni, J. F. and Lundin, F. E., Jr. 1966. Infective hepatitis and Down's syndrome. Lancet 1:712-713.

110. Stark, C. R. and Mantel, N. 1967. Lack of seasonal- or temporal-spatial clustering of Down's births in Michigan. Am. J. Epidemiol. 86:199-213.

111. Ceccarelli, G. and Torbidoni, L. 1967. Viral hepatitis and Down's syndrome. Lancet 1:438

112. Dallaire, L. and Kingsmill-Flynn, D. 1967. Infectious hepatitis and Down's syndrome. Lancet 2:467.

113. Kogon, A., Kronmal, R. and Peterson, D. R. 1967. Viral hepatitis and Down's syndrome. Lancet 1:615.

114. Mella, B. and Lang, D. 1967. Leukocyte mitosis: suppression in vitro associated with acute infectious hepatitis. Science 155:80-81.

115. Kogon, A., Kronmal, R. and Peterson, D. R. 1968. The relationship between infectious hepatitis and Down's syndrome. Am. J. Public Health 58:305-311.

116. Baird, P. A. and Miller, J. R. 1968. Some epidemiological aspects of Down's syndrome in British Columbia. Brit. J. Prev. Soc. Med. 22:81-85.

117. Pergament, E. 1969. Epidemicity of chromosome aberrations: an assessment of epidemiological investigations on chromosome aberrations. Chic. Med. Sch. Q. 28:57-66.

118. Blumberg, B. S., Gerstley, B. J., Sutnick, A. I., Millman, I. and London, W. T. 1970. Australia antigen, hepatitis virus and Down's syndrome. Ann. N. Y. Acad. Sci. 171:486-499.

119. Doxiadis, S., Pantelakis, S., and Valaes, T. 1970a. Down's syndrome and infectious hepatitis. Lancet 1:897.

120. ______________________. 1970b. Infectious hepatitis and Down's syndrome. Lancet 2:826.

121. Kucera, J. 1970. Down's syndrome and infectious hepatitis. Lancet 1:569-570.

122. Pergament, E. 1970. Down's syndrome and infectious hepatitis. Lancet 2:1192.

123. Pantelakis, S. N., Chryssostomidou, O. M., Alexiou, D., Valaes, T. and Doxiadis, S. A. 1970. Sex chromatin and chromosome abnormalities among 10,412 live born babies. Arch. Dis. Child. 45:87-92.

124. Stark, C. R. and Rudzki, C. 1970. Infectious hepatitis and Down's syndrome. Lancet 2:572-573.

125. Walker, F. A. 1970. Epidemic of Down's syndrome? Lancet 1:1059.

126. Nichols, W. N. 1970. Viruses and chromosomal abnormalities. Ann. N. Y. Acad. Sci. 171:478-485.

127. Kucera, J. 1971. Infectious hepatitis and Down's syndrome. Lancet 1:549.

128. Baer, P. N., Coccaro, P. J., Baer, M. J. and Kilham, L. 1971. Craniofacial manifestations of virus induced mongolism in the hamster and Down's syndrome in man. Am. J. Orthod. 60:221-234.

129. Shapiro, L. R., Redner, W. J. and Innella, F. P. 1971. Australia antigen and Down's syndrome. Lancet 2:215.

130. Dallapiccola, B. 1971. Australia antigen and Down's syndrome. Lancet 2:548.

131. Dietzman, D. E., Madden, D. L., Sever, J. L., Lander, J. J. and Purcell, R. H. 1972. Lack of relationship between Down's syndrome and maternal exposure to Australia antigen. Am. J. Dis. Child. 124:195-197.

132. Slater, B. S., Watson, G. I. and McDonald, J. C. 1964. Seasonal variation in congenital abnormalities: preliminary report of a survey conducted by the Research Committee of Council of the College of General Practitioners. Br. J. Prev. Soc. Med. 18:1-7.

133. Lander, E., Forssman, H. and Akesson, H. 1964. Season of birth and mental deficiency. Acta. Genet. (Basel) 14:265-280.

134. Robinson, A. and Puck, T. 1967. Studies in chromosomal nondisjunction in man II. Am. J. Hum. Genet. 19:112-129

135. Jongbloet, P. H. 1971. Month of birth and gametopathy: an investigation into patients with Down's, Klinefelter's and Turner's syndrome. Clinical Genetics 2:315-330.

136. McDonald, A. D. 1972. Yearly and seasonal incidence of mongolism in Quebec. Teratology 6:1-4.

137. Harlap, S. 1974. A time-series analysis of the incidence of Down's syndrome in West Jerusalem. Am. J. Epidemiol. 99:210-217.

138. Haynes, S. G., Gibson, J. B. and Kurland, L. T. 1974. Epidemiology of neural-tube defects and Down's syndrome in Rochester, Minnesota, 1935-1971. Neurology 24:691-700.

139. Gentry, J. T., Parkhurst, E. and Bulin, G. V. 1959. An epidemiological study of congenital malformations in New York State. Am. J. Public Health 49:497-513.

140. Uchida, I. A. and Curtis, E. J. 1961. A possible association between maternal radiation and mongolism. Lancet 2:848-850.

141. Carter, C., Evans, K. and Stewart, A. 1961. Maternal radiation and Down's syndrome. Lancet 2:1042.

142. Schull, W. J. and Neel, J. V. 1962. Maternal radiation and mongolism. Lancet 1:537-538.

143. Uchida, I. A., Holunga, R. and Lawler, C. 1968. Maternal radiation and chromosomal aberrations. Lancet 2:1045-1049.

144. Schuman, L. M. and Gullen, W. H. 1970. Background radiation and Down's syndrome. Am. N. Y. Acad. Sci. 171:441-453.

145. Stevenson, A. C., Mason, R. and Edwards, K. D. 1970. Maternal diagnostic x-irradiation before conception and the frequency of mongolism in children subsequently born. Lancet 2:1335-1337.

146. Wald, N., Turner, H. and Borges, W. 1970. Down's syndrome and exposure to x-irradiation. Ann. N. Y. Acad. Sci. 171:454-465.

147. Awa, A. A. and Honda, T. 1971. Chromosome-aberration frequency in cultured blood cells in relation to radiation dose of A-bomb survivors. Lancet 2:903-905.

148. Mason, R. 1971. Maternal diagnostic x-irradiation before conception. Nurs. Times 67:378-379.

149. Uchida, I. A. 1971. Trisomy associated with diagnostic x-rays. South Med. J. 64:81-84.

ed in "any A" and again in "any B".

150. Alberman, E., Polani, P. E., Fraser Roberts, J. A., Spicer, C. C., Elliott, M. and Armstrong, E. 1972. Parental exposure to x-irradiation and Down's syndrome. Ann. Hum. Genet., Lond. 36:195-208.

151. Alberman, E. D. 1973. Maternal x-radiation and chromosome abnormalities in subsequent conceptions. Br. J. Prev. Soc. Med. 27:67-68.

152. Holmberg, M. 1974. No interaction between ultraviolet and x-irradiation on chromosome aberrations in cells with trisomy 21. Nature 249:448-449.

153. Barron, C. I., Love, A. A. and Baraff, A. A. 1955. Physical evaluation of personnel exposed to microwave emanations. J. Aviation Med. 26:442.

154. Ely, T. S., Goldman, D. E., Hearnon, J. Z., Williams, R. B. and Carpenter, H. M. 1957. Heating characteristics of laboratory animals exposed to 10 cm microwaves. U. S. Naval Medical Research Institute Research Report, Project NM 001 256.13.02, 15.

155. Barron, C. I. and Baraff, A. A. 1958. Medical considerations of exposure to microwave (radar). J.A.M.A. 168:1194.

156. Mickey, G. 1963. Electromagnetism and its effect on the organism. N. Y. State J. Med. 63:1935.

157. Van Ummersen, C. A. 1963. An experimental study of developmental abnormalities induced in the chick embryo by exposure to radio frequency waves. Ph.D. dissertation, Dept. Biol., Tufts University, Medford, Mass.

158. Rose, V. E., Gellin, G. A., Powell, C. H. and Bourne, H. G. 1969. Evaluation and control of exposures in repairing microwave ovens. Amer. Ind. Hyg. Assoc. J. 30:137-142.

159. Cleary, S. F. 1970. Biological effects of microwave and radiofrequency radiation. Critical Reviews in Environmental Control 1:257-305.

160. Heller, J. H. 1970. In Biological effects and health implications of microwave radiation. U. S. Government Printing Office, Washington, D.C.

161. Marha, K. 1970. In biological effects and health implications of microwave radiation. U. S. Government Printing Office, Washington, D.C.

162. Michaelson, S. M. 1971. Biomedical aspects of microwave exposures. Am. Ind. Hyg. Assoc. J. 32:338-345.

163. Odland, L. T. 1972. Observations on microwave hazards to USAF personnel. J.O.M. 14:544-547.

164. McRee, D. I. 1972. Environmental aspects of microwave radiation. Environmental Health Perspectives. 41-53.

165. Cleary, S. F. 1973. Uncertainties in the evaluation of the biological effects of microwave and radiofrequency radiation. Health Physics 25:387-404.

166. Tolgskaya, M. S. and Gordon, Z. V. 1973. Pathological Effects of Radio Waves. Consultants Bureau, N.Y.

167. Varma, M. M. and Traboulay, E. A., Jr. 1975. Biological effects of microwave radiation on the testes of Swiss mice. Experientia. 31:301-302.

168. Richards, B. W., Stewart, A. and Sylvester, P. E. 1965. Reciprocal translocation and mosaicism in a mongol. J. Ment. Defic. Res. 9:118-124.

169. Stoeckenius, M. 1966. D/G translocation in Down's syndrome. Lancet 1: 1208-1209.

170. Hubner, H., Jeske, J. and Dzida, J. 1969. Familial Down's syndrome with G/G translocation. Bull. Pol. Med. Sci. Hist. 12:164-167.

171. Moric-Petrovic, S., Laca, Z. and Kalicanin, P. 1972. Down's syndrome with an atypical G/G translocation derived from familial pericentric inversion in one chromosome of the G group. J. Med. Genet. 9:478-482.

172. Hecht, F., McCaw, B. K., Howard, P., Stoddard, G. and Seely, J. 1973. 21/21 translocation: correlation of banding with meiotic results. Humangenetik 20:269-271.

173. Hahnemann, N. and Eiberg, H. 1973. Antenatal genetic diagnosis in a kindred with a 15+ chromosome. Clinical Genetics 4:464-473.

174. Chapman, C. J., Gardner, R. J. M. and Veale, A. M. O. 1973. Segregation analysis of a large t(21q, 22q) family. J. Med. Genet. 10:362-366.

175. Furbetta, M., Falorini, A., Antignani, P. and Cao, A. 1973. Sibship (21q, 21q) translocation Down's syndrome with maternal transmission. J. Med. Genet. 10:371-375.

176. Niebuhr, E. 1974. Down's syndrome: the possibility of a pathogenetic segment on chromosome #21. Humangenetik 21:99-101.

177. Lundsteen,C., Vestermark, S. and Philip, J. 1974. A familial, balanced 2/5 translocation associated with trisomy 21 in one individual. Human Hered. 24:88-94.

178. Gardner, R. J. M. and Veale, A. M. O. 1974. De noro translocation Down's syndrome: risk of recurrence of Down's syndrome. Clinical Genetics 6:160-164.

179. Chaganti, R. S. K., Morillo-Cucci, G., Degnan, M. and German, J. 1975. Mongolism by tertiary trisomy. Lancet 1:698-699.

180. Williams, J., Summitt, R., Martens, P. and Kimbrell, R. 1975. Familial Down's syndrome due to t(10; 21) translocation. Evidence that the Down phenotype is related to trisomy of a specific segment of chromosome 21. Am. J. Hum. Genet. 27:478-485.

181. Clark, C. M., Edwards, J. H. and Smallpiece, V. 1961. 21-trisomy/normal mosaicism in an intelligent child with some mongoloid characteristics. Lancet 1:1028-1030.

182. Blank, C. E., Gemmell, E., Casey, M. D. and Lord, M. 1962. Mosaicism in a mother with a mongol child. Brit. Med. J. 2:378-380.

183. Smith, D. W., Therman, E. M., Patau, K. A. and Inhorn, S. L. 1962. Mosaicism in the mother of two mongoloids. Am. J. Dis. Child. 104: 534.

184. Zellweger, H. and Abbo, G. 1963. Chromosomal mosaicism and mongolism. Lancet 1:827.

185. Weinstein, E. D. and Warkany, J. 1963. Maternal mosaicism and Down's syndrome (mongolism). J. Pediat. 63:599-604.

186. Verresen, H., Van den Berghe, H. and Creemers, J. 1964. Mosaic trisomy in phenotypically normal mother of mongol. Lancet 1:526-527.

187. Day, R. W. and Wright, S. W. 1965. Down's syndrome at young maternal ages: chromosomal and family studies. Pediatrics 66:764-771.

188. Chitham, R. G. and MacIver, E. 1965. A cytogenetic and statistical survey of 105 cases of mongolism. Ann. Hum. Genet. 28:309-315.

189. Gianelli, F., Hamerton, J. F. and Carter, C. O. 1965. Cytogenetics of Down's syndrome (mongolism). II. The frequency of interchange trisomy in patients born at a maternal age of less than 30 years. Cytogenetics 4:186-192.

190. Hamerton, J. L., Giannelli, F. and Polani, P. E. 1965. Cytogenetics of Down's syndrome (mongolism). I. Data on a consecutive series of patients referred for genetic counselling and diagnosis. Cytogenetics 4:171-185.

191. Ridler, M. A., Shapiro, A., Delhanty, J. D. and Smith, G. F. 1965. A mosaic mongol with normal leukocyte chromosomes. Brit. J. Psychiat. 111:183-185.

192. Zellweger, H., Abbo, G., Nielsen, N. and Wallwork, K. 1966. Mosaic mongolism with normal chromosomal complement in the white blood cells. Hum. Genet. 4:323-327.

193. Mikkelsen, M. 1966. Familial Down's syndrome. A cytological and genealogical study of twenty-two families. Ann. Hum. Genet. 30:125-146.

194. Edgren, J., De la Chapelle, A. and Kaariainen, R. 1966. Cytogenetic study of seventy-three patients with Down's syndrome. J. Ment. Defic. Res. 10:47-62.

195. Aarskog, D. 1969. Down's syndrome transmitted through maternal mosaicism. Acta. Paediact. Scand. 58:609-614.

196. Richards, B. W. 1969. Mosaic mongolism. J. Ment. Defic. Res. 13:66-83.

197. ____________. 1970. Observations on mosaic parents of mongol propositi. J. Ment. Defic. Res. 14:342-346.

a.) Secondary Constriction; b.) Quadriradial; c.) Dicentric; d.) Fragment; e.) Isochromatid Break; f.) Gap

198. Krmpotic, E. and Hardin, B. M. 1971. Secondary nondisjunction causing regular trisomy-21 in the offspring of a mosaic trisomy-21 mother. Am. J. Obstet. Gynecol. 110-589-590.

199. Hsu, L. Y. F., Gertner, M. Leiter, E. and Hirschhorn, K. 1971. Paternal trisomy 21 mosaicism and Down's syndrome. J. Med. Genet. 23: 592-601.

200. Priest, J. H., Verhulst, C. and Sirkin, S. 1973. Parental dermatoglyphics in Down syndrome. A ten year study. J. Med. Genet. 10:328-332.

201. Mehes, K. 1973. Paternal trisomy 21 mosaicism and Down's anomaly. Humangenetik 17:297-300.

202. Richards, B. W. 1974. Investigation of 142 mosaic mongols and mosaic parents of mongols; cytogenetic analysis and maternal age at birth. J. Ment. Defic. Res. 18:199-208.

203. Buhler, E. M., Kosztolanyi, G. and Stalder, G. R. 1975. Possible mosaic XXX-XXY marriage with abnormal offspring. Lancet 1:334.

204. Smith, D. W. 1961. Autosomal trisomy syndromes. Lancet 2:211-212.

205. Pozsonyi, J. 1965. Biochemical consequences of supernumerary chromosome subtype in mongolism. Am. J. Ment. Defic. 70:213-217.

206. Robinson A. and Puck, T. T. 1965. Sex chromatin in new borns: presumptive evidence for external factors in nondisjunction. Science 148:83-85.

207. Brogger, A. 1966. Double fertilization in Down's syndrome. Lancet 1: 1270-1271.

208. Polani, P. E. 1966. Chromosome anomalies and abortions. Dev. Med. Child. Neurol. 8:67-70.

209. Huang, S., Emanuel, I., Lo, J., Kiao, S. and Hsu, C. 1967. A cytogenetic study of 77 Chinese children with Down's syndrome. J. Ment. Defic. Res. 11:147-152.

210. Hecht, F. and Weleber, R. 1967. Trisomy 21 or 22 in Down's syndrome? Lancet 2:467.

211. Ebbin, A. J., Heath, C. W. Moldow, R. E. and Lee, J. 1968. Down's syndrome and leukemia in a family. J. Ped iatr. 73:917-920.

212. Milunsky, A. 1968. Cystic fibrosis and Down's syndrome. Pediatrics 42:501-503.

213. Kahn, J. and Abe, K. 1969. Consistent and variable chromosome anomalies in parents of children with Down's syndrome. J. Med. Genet. 6:137-149.

214. Hegurashi, M. 1969. Down's syndrome: chromosome analysis in 321 cases in Japan. J. Med. Genet. 6:401-404.

215. Juberg, R. C. and Davis, L. M. 1970. Etiology of nondisjunction: lack of evidence for genetic control. Cytogenetics 9:284-293.

216. Lubs, H. A. and Ruddle, F. H. 1970. Chromosomal abnormalities in the human population: estimation of rates based on New Haven newborn study. Science 169:495-497.

217. Fabia, J. and Drolette, M. 1970. Malformations and leukemia in children with Down's syndrome. Pediatrics 45:60-70.

218. Kucera, J. 1971. Leukemia and twinning tendency in families of children with Down's syndrome. J. Ment. Defic. Res. 15:77-80.

219. Ali-Aish, M. S., Dodson, W. E. and Plato, C. C. 1971. Down's syndrome with XYY: 48, XYY, G+. Am. J. of Dis. Child: 121:444-446.

220. Benson, P. F. 1971. Biochemical abnormalities in chromosome anomalies. Lancet 2:1200-1201.

221. Singer, J., Sachdeva, S., Smith, G. F. and Hsia, D. Y. Y. 1972. Triple X female and a Down's syndrome offspring. J. Med. Genet. 9:238-239.

222. Schmidt, R., Mundel, G., Rosenblatt, M. and Katznelson, M. 1972. Apparent G-monosomy, G-deletion, and incomplete Down's syndrome in a single family. J. Med. Genet. 9:457-461.

223. Hongell, K. and Airaksinen, E. 1972. A Gq deletion in a girl with Down's syndrome. Hum. Hered. 22:80-85.

224. McClure, H. M. 1972. Animal model-trisomy in a chimpanzee. Am. J. Pathol. 67:413-416.

225. Lynch, D. A., Neu, R. L. and Gardner, L. I. 1972. Nondisjunction in males: commoner than suspected? J.A.M.A. 222:1311-1312.

226. Bloom, A. D. 1972. Induced chromosomal aberrations in man. 1972. Advances in Human Genetics 3:99-172.

227. Robinson, J. A. 1973. Origin of extra chromosome in trisomy 21. Lancet 1:131-133.

228. Smith, G. F. and Sachdeva, S. 1973. Origin of extra chromosome in trisomy 21. Lancet 1:487.

229. Cotton, J. E., Kaplan, A. R. and Zsako, S. 1973. Acrocentric chromosomes in cultured leukocytes from mothers of children affected with the G1-trisomy syndrome. Am. J. of Mental Def. 78:249-254.

230. Curtis, D. J. 1974. Acrocentric associations in mongol populations. Humangenetik 22:17-22.

231. Evans, H. J. and O'Riordan, M. L. 1975. Human peripheral blood lymphocytes for the analysis of chromosome aberrations in mutagen tests. Mutat. Res. 31:135-148.

232. Broustet, A., Serville, F., Roger, R. and Gachet, M. 1975. X monosomy and 21-trisomy in a sibship. Humangenetik 27:333-337.

APPENDIX A

APPENDIX A-a CONTRACTORS PROPOSAL FOR CURRENT STUDY

APPENDIX A-b CONTRACTORS PROPOSAL FOR EXTENSION OF CURRENT STUDY

APPENDIX A-a

CONTRACTORS PROPOSAL FOR CURRENT STUDY

APPENDIX A
Part a

CONTRACTOR'S PROPOSAL FOR CURRENT STUDY SPRING, 1969

Parental Radiation Exposure and Down's Syndrome, with Particular Attention to Ionizing Radiation and Radar

(Revised 4/25/69 - Confined to Baltimore Metropolitan Area)

Purpose: To determine whether the parents of mongols differ from the parents of matched normal controls with regard to exposure to radar and/or ionizing radiation and to examine the chromosomes of those radar-exposed parents and corresponding parents from the matched series for any discernible differences and/or abnormalities.

Specific Aims:

1. To compare the parents of mongols with those of controls with regard to reported radar exposure, occupations involving radar exposure or exposure to any sources of radioactive substances or radiation.
2. To compare mothers and fathers of Down's syndrome cases with mothers and fathers of matched controls with regard to medical radiation (diagnostic and/or therapeutic) exposure.
3. To compare the parents of mongols and of controls with regard to other factors (socioeconomic status, religion, menstrual and medical history, marital history etc.) recognized or suspected to be associated with the occurrence of Down's syndrome and to examine their possible interaction with radar and/or ionizing radiation exposure.
4. To examine the chromosomes of the fathers (or mothers) with a history of exposure to radar and the fathers (or mothers) of children matched to them, and to compare them.

Method of Procedure

I. Subjects

Selection of cases. Children with a diagnosis of mongolism and born

after January 1, 1945 in the greater Baltimore area ascertained from the Maryland State Training School, other special institutions for the retarded in the Baltimore Metropolitan area including special private, county, parochial, and public schools, Baltimore area hospitals and private physicians.

Since a similar previous study has been carried out in the Baltimore area, the interview sample will be confined to those cases not ascertained in the previous study. From 1/1/1946 to 10/1/1962, 421 cases were collected in the previous Baltimore area study, with 288 meeting the study requirements and 216 available for interview. At the same rate of 1.4 per month meeting requirements and 1.07 per month available for interview, it is estimated that approximately 105 additional mongols may be obtained for the Baltimore area from 10/1/62 - 1/1/69 (with at least 80 available for final study). If 1945 is added approximately, 13-16 more cases would be available.

Diagnostic criteria: The following set of physical criteria for Down's syndrome based on consistently observed findings (See Table 1) as previously reported will be considered "primary" criteria:

Brachycephaly
Slanted palpebral fissures
Epicanthic folds
Palmar simian lines
Malformed ears
Broad and/or short neck
Malformed fingers and/or hands
Nasal abnormality
Hypertelorism
Abnormal palate
Brushfield spots
Broad and/or short trunk

TABLE I

Physical findings in cases of Down's syndrome (from Sigler, Lilienfeld, Cohen, Westlake, 1965)

Physical signs	Physical signs present No.	%
Brachycephaly	169	87.1
Slanted palpebral fissures	177	91.2
Epicanthic folds	155	79.9
Palmar simian lines	126	64.9
Malformed ears	160	82.5
Broad and/or short neck	147	75.8
Malformed fingers and/or hands	156	80.4
Nasal abnormality	177	91.2
Hypertelorism	186	95.9
Abnormal palate	164	84.5
Brushfield spots	107	55.2
Broad and/or short trunk	159	82.0

Selection of control subjects: The birth certificates of the children with Down's syndrome will be located and their place of birth and other vital information verified. Control subjects will then be selected by rigidly matching, in a systematic manner, each case with another certificate for (1) hospital of birth (or at home); (2) sex of child (3) maternal age at time of birth of child and (4) date of birth.

In each case the best control would be a child whose birth date was closest to that of the Down's child of the same sex born in the same hospital to a mother of the same age. If the best control on the basis of established criteria either has left the state or cannot be located, the next best control will be selected - i.e. with slightly greater difference in birth dates - the other criteria remaining the same.

The hospital records as well as birth certificates of all control children will be examined to be certain that the "normal" control group contains no cases of Down's syndrome.

II. Data to be Collected:

A. Hospital, medical and vital records

Birth records - certificate and hospital and other available hospital and medical records will be examined for pertinent information.

B. Interviews

Mothers, and, wherever possible, fathers, will be interviewed to obtain further information. Where mothers or fathers are deceased, information will be obtained insofar as possible from the surviving parent. Where both parents are deceased, the subject will be excluded from the matched series but analyzed in a special study series.

1. Interview data will include:

   Complete names and addresses of each parent, index child and sibs.

   Child's sex, place of birth, physician and history of hospitalization and medical conditions.

   Mother's residence, occupation, education & religion, marital, menstrual, pregnancy, medical and other pertinent data including hospitalization history and detailed information about radiation exposure: diagnostic including parts of body x-rayed, radiation therapy for a list of conditions, fluoroscopy, injection or ingestion of radioactive substances, medication.

   Father's residence, occupation history (with more detailed information about radiation and radar exposure and military service), marital history, number of offspring, illness, medical and hospitalization history and other pertinent data.

2. Method of interviewing

   The mother and father will usually be interviewed independently at home. The approach to both the families of the mongols and controls will be uniform; the interviewers will not be informed which are cases and controls and recognition of the Mongol's family will usually not be known until the actual interview is conducted, if then. Questions about radar and radiation exposure, medical conditions, occupation will be phrased without reference to the birth of the index child, though approximate dates will be obtained so that the time relationships relative to the index child can be examined in the analysis.

3. Validation of findings derived from interview data will be attempted by independent and simultaneous examination of several characteristics of parents of mongols and of controls through an independent search of hospital records. A list of every parental name in the study (married and maiden) will be submitted to every Baltimore and Washington area

hospital to obtain documentation of those characteristics independently and irrespective of information obtained on interview. If any records at the hospitals are available for these persons, the charts will be reviewed for medical diagnosis during outpatient visits and inpatient stays, surgical procedures and x-ray and other radiation exposure. The interview and the hospital record findings will then be compared.

C. Chromosome studies

The chromosomes of fathers who reported a history of radar exposure will be examined to determine whether any aberrations - aneuploidy, breaks, etc. - are noted. As a comparison group the chromosomes of fathers of the children matched to those whose fathers indicated radar exposure will also be studied.

In the series already published (Sigler, Lilienfeld, Cohen & Westlake) 18 fathers of children with Down's syndrome and 7 fathers of control children reported definite radar exposure with several additional fathers (8) having questionable exposure. These 25-33 fathers and the 25-33 fathers of children matched to those cases and controls will be located and bloods drawn for chromosome analysis. It is estimated that the similar study planned to collect cases from 10/1/62 - 1/1/69 in the Baltimore area with the inclusion of 1945 should yield at least 11 additional exposed fathers and 11 matched fathers or a total of 72-80 fathers on whom chromosome studies will be carried out. This estimate assumes that the rate of Down's syndrome, radar exposure and ascertainment will be similar for the years to be studied in comparison with those years already examined.

The numbers involved are indicated on the accompanying table. There is an additional small number, from the previous samples, who indicated that they had worked near radar or had had some radar exposure which was judged questionable and therefore not included in the original series judged to be definitely radar exposed. It would be desirable, if possible, to study this group of "possible or questionable exposures" to determine whether they differ in any way from the non-exposed persons.

ADDITIONAL MONGOLISM CASES EXPECTED

	No. of Months	No. ascertained at 2.1/mo.	No. meeting criteria at 1.4/mo.	No. available for interview at 1.1/mo.	Total fathers exposed to radar (.116)*	Total fathers of cases exposed (.083)	Total fathers exposed and matched controls
Baltimore, 1945	12	25.2	16.8	13.2	1.5	1.0	3.0
Baltimore, 10/1/62 - 1/1/69	75	157.2	105.0	82.5	9.6	6.2	19.2
Additional Baltimore	87	182.7	121.8	95.7	11.1	7.2	22.2
Baltimore obtained 1/1/46 - 10/1/62	201	422	288	216	25	18	50
Total sample	287	604.7	409.8	311.7	36.1	25.2	72.2

Assumes same proportion exposed as in previous Baltimore sample: i.e. 18 case fathers and 7 control fathers from 216 cases and 216 matched controls.

In summary, the funds requested will be used to:

1. Locate the fathers of cases and controls who had reported radar exposure in the 1/1/46 - 10/1/62 series and:
   A. Bring their records up to date obtaining more detailed information of exposure and their experience since our last contact.
   B. Obtain blood samples for chromosome studies.
   C. Carry out complete chromosome analysis on these fathers.
2. Locate the fathers of cases and controls matched to the radar exposed subjects and carry out the same procedures (A, B, AND C indicated above) for these fathers.
3. Identify and trace children with Down's syndrome born in the Baltimore area from 10/1/62 to 1/1/69 as well as 1/1/45 - 12/31/45 and:
   A. Verify diagnosis
   B. Search birth certificates on these affected children
   C. Select controls matched to ascertained cases by hospital, date of birth, maternal age, race and sex of infant.
4. Carry out interviews of parents of Down's cases.
5. Trace selected matched controls and similarly interview their parents.
6. Obtain blood samples and carry out chromosome analysis on all fathers (or mothers) reporting radar exposure and on the corresponding fathers (or mothers) of children matched to those whose parents were exposed.

APPENDIX A-b

CONTRACTORS PROPOSAL FOR EXTENSION OF CURRENT STUDY

APPENDIX A
Part b

CONTRACTOR'S PROPOSAL FOR EXTENSION OF CURRENT STUDY WINTER 1969-1970

PARENTAL RADIATION EXPOSURE AND DOWN'S SYNDROME (MONGOLISM) WITH PARTICULAR ATTENTION TO IONIZING RADIATION AND RADAR

Purpose:

To extend the investigation of (1) radar and/or ionizing radiation exposure of parents of mongols and of parents of their matched controls and (2) possible chromosomal aberrations among fathers radar exposed and unexposed by including a series approximately 50% larger than originally estimated.

The Specific Aims indicated below, remain the same as previously specified but are now to encompass investigation of approximately 140 or more cases of Down's syndrome and an equal number of families of matched control subjects instead of the original estimate of 95 cases and 95 controls:

1. To compare the parents of mongols with those of controls with regard to reported radar exposure, occupations involving radar exposure, or exposure to any occupational or military sources of radioactive substances or radiation.

2. To compare parents of Down's syndrome cases with parents of matched controls with regard to medical radiation exposure (diagnostic and/or therapeutic): e.g. individual x-ray photographs, fluoroscopic radiation, ingestion or injection of radioactive substances such as ^{131}I, ^{32}P etc.; implantation of radon seeds; cobalt radiation, and any other diagnostic or therapeutic procedures involving ionizing radiation.

3. To compare the parents of mongols and of controls with regard to other factors (socioeconomic status, religion, menstrual and medical history, marital history, etc.) recognized or suspected to be associated with the occurrence of Down's syndrome and to examine the possible interaction of such factors with radar and ionizing radiation exposure.

4. To examine the chromosomes of the fathers with a history of exposure to radar and the fathers of children matched to them, and to compare findings.

UNDERLYING RATIONALE AND BACKGROUND OF STUDY:

In an epidemiological study of the parents of children with Down's syndrome born from January 1, 1946 to September 30, 1962 and parents of matched control children, a significantly larger percentage of fathers of Down's cases reported radar exposure than control fathers.[1] Moreover, a larger percentage of the fathers of Down's cases reported having been in military service (63.1 percent versus 56.6 percent for control fathers), but this difference was not statistically significant. Because of the possible implications of these findings with regard to the risk of Down's syndrome and possibly other genetic damage to progeny, as well as somatic damage in exposed individuals, further studies of the effects of exposure to radar have been undertaken.

In addition, since the initiation of this presently ongoing phase on June 1, 1969, certain opportunities to extend the scope of this investigation have become apparent: firstly in regard to obtaining more objective validation of the military service and radar exposure on all fathers - original and current series - irrespective of reported service and/or exposure; and secondly in regard to increasing the size of the current study series.

Validation of military service and exposure:

Through consultation on procedures for checking military service and radar exposure from government military files, a plan has been designed for documentation of military service and radar exposure. This is to be carried out along with supplemental interview information by partial follow-up reinterview of the original series. Moreover, even in the absence of available reinterview data validation procedures will be applied. Thus the search of government records on fathers will be entirely independent on whether or not service or radar exposure was reported.

Increased size of study series: It is now apparent that a larger study series than expected will be available. Whereas it was estimated that the families of approximately 95 cases and 95 controls would be available for the current study, more comprehensive methods of ascertainment, probably improved diagnosis and more complete case-finding by community and private agencies as well as practicing physicians, has made it possible to identify over 142 cases for study, thus a 50% larger sample.

The likelihood of attaining more definitive results would be considerably enhanced both by being able (1) to include the total study series available rather than the previously estimated smaller study group, and (2) to carry out more intensive search and validation of military service records and radar exposure.

For these purposes, therefore, an extension of the time schedule for six months beyond the original date and additional funds will be required to accomodate the 50% larger sample. The budget for supplementary funds is attached. It should be noted also that while the changing circumstances leading to improved ascertainment in the time interval between the original and current investigation has made possible an increased yield of cases, other changes, such as these pertaining to residential patterns of families of children born in metropolitan Baltimore hospitals have increased the travel time and cost per case studied, as explained in the first Progress Report [(2)] (Attached as Appendix I).

In the extended plan, both the documentation of military service records and addition of the larger series for study are to be incorporated within the framework of the existing project design, a composite of three interdependent substudies which have been initiated and are being carried out simultaneously:

(1) the original interview study series;

(2) current interview study series; and

(3) chromosome studies

As now proposed, they would encompass the following:

(1) Original interview substudy - original interview study series (families of 216 Down's syndrome children born 1/1/46 - 9/30/62 and their 216 matched controls). Not only are fathers who reported radar exposure and their matched subjects being traced and studied for chromosome abnormalities, but also partial reinterview for more detailed military data and possibly missed radar information as well as independent search of government military service records for validation of information on all fathers irrespective of whether they reported military or radar exposure are to be carried out.

(2) Current interview substudy - current interview study series (families of Down's cases born in 1945 and between 10/1/62 - 12/31/68): Identification of cases, control matching, tracing and complete interviewing are being carried out as in the original study series, with supplementary detailed data collection on military service and radar exposure of fathers. In addition, independent validation of military service and radar exposure from government files is to be carried out on this series as on the original series indicated above. This current study series is to include the revised larger estimate of 280-284 families.

(3) Chromosome Study - All fathers in the original and current interview study series reporting radar exposure and fathers of children matched to the children of those radar exposed fathers are being followed up and samples of peripheral blood examined for chromosome abnormalities. In addition, the chromosome study group includes radar exposed fathers ascertained for the original and current series but not in the final interview study series because of unavailability of the complete matched pair for interview. For these unmatched radar exposed fathers (unmatched in the interview series) a new unexposed match is being obtained for chromosome analysis.

METHODS OF PROCEDURE

The method of procedure follows the overall design proposed and approved for the project in progress, with the supplementary aspects indicated above.

I. Subjects

Selection of cases: Children with a diagnosis of mongolism meeting the criteria already described for the "original" series [1] and born in the greater Baltimore area between 1/1/45 and 12/31/45 and also those born 10/1/62 through 12/31/68 are included. Sources of ascertainment for the original series and for the current series have been indicated. [1,2]

The current interview sample is being confined to those years for which cases were not ascertained in the original series. In that previous study, 421 cases born from January 1, 1946 to October 1, 1962 were collected, with 288 meeting the study requirements and 216 available for interview. At the same rate of 1.4 per month meeting requirements and 1.07 per month available for interview, it was estimated that approximately 105 additional mongols would be found in the Baltimore area from October 1, 1962 to January 1, 1969, with at least 80 available for final study. If 1945 were added, 13 to 16 more cases would be available, thus approximately 95 cases in all.

Because of the increased number of sources of ascertainment as well as better diagnostic procedures and case finding techniques among physicians, private and public agencies, and possibly also improved searching techniques, it has been possible, as stated above, to obtain a larger study series than previously anticipated, i.e. about 142 cases of Down's syndrome and an equal number of matched controls rather than the 95 of each previously estimated.

Diagnostic criteria

The following physical findings in Down's syndrome, based on previously reported findings are considered "primary" criteria for diagnosis:

1. Brachycephaly
2. Slanted palpebral fissures
3. Epicanthic folds
4. Palmar simian lines
5. Malformed ears
6. Broad and/or short neck
7. Malformed fingers and/or hands
8. Nasal abnormality
9. Hypertelorism
10. Abnormal palate
11. Brushfield spots
12. Broad and/or short trunk

Selection of control subjects. Birth certificates of the children with Down's syndrome are being located, and their place of birth and other vital information verified. Control subjects are selected by rigidly matching, in a systematic manner, each case with another certificate for (1) hospital of birth (or at home), (2) sex and race of child, (3) maternal age at time of birth of child and (4) date of birth.

In each case the best control is a child whose birth date was closest to that of the Down's child of the same sex born in the same hospital to a mother of the same age. If the best control on the basis of established criteria either has left the state or cannot be located, the next best control is selected (i.e., with slightly greater difference in birth dates), the other criteria remaining the same.

The hospital records as well as birth certificates of all control children are examined to be certain that the "normal" control group contains no case; of Down's syndrome.

II. Data to be Collected

Records. Birth records (certificate and hospital) and other available hospital and medical records are examined for pertinent information.

Interviews. Mothers, and fathers, are being interviewed to obtain further information. Where mothers or fathers are deceased, information is obtained insofar as possible from the surviving parent. Where both parents are deceased, the subject is excluded from the matched series but analyzed in a special study series.

Interview data include:

1. Complete names and addresses of each parent, index child and sibs.

2. Child's sex, place of birth, physician, and history of hospitalizations and medical conditions.

3. Mothers' education; religion; and histories of residence, occupation and marriage. Medical data will include histories of menstruation, pregnancy, hospitalization and details of radiation exposure. The latter will include diagnostic X-ray, radiation therapy, fluoroscopy, and injection or ingestion of radioactive substances.

4. Fathers' residence; occupational history with detailed information about military service; marital history; number of offspring; illnesses; medical and hospitalization histories; and other pertinent data.

The mother and father *are usually interviewed* independently at home. The approach to both the families of the mongols and controls are uniform; the interviewers are not informed which are cases and controls and recognition of the mongol's family is usually not known until the actual interview is conducted, if then. Questions about radar and radiation exposure, medical conditions, and occupation are phrased without reference to the birth of the index child. Insofar as possible, dates of exposure are obtained, however, so that the time-relationships relative to the index child can be examined in the analysis.

Validation of findings derived from interview data is being attempted by independent and simultaneous examination of several characteristics of the parents of mongols and of controls as well as through independent search of hospital records.

Validation procedures for military service/radar exposure include the above described independent ascertainment of data through search of military files on all fathers, irrespective of whether they reported such service/exposure or not.

Chromosome Studies:

The chromosomes of fathers who report a history of radar exposure are being examined to determine whether any aberrations, such as aneuploidy, translocations, dicentrics or other aberrations or evidence of breaks, etc., are observed. As a comparison group, the chromosomes of unexposed fathers of the children matched to those whose fathers indicated radar exposure are also being studied.

In the series already published [1] 18 fathers of children with Down's syndrome and seven fathers of control children reported definite radar exposure with several additional fathers (plus or minus eight) having questionable exposure. These 25 to 33 fathers and the 25 to 33 fathers of children matched to those cases and controls are being located and blood drawn for chromosome analysis.

It was estimated that the current study series (based on cases born Oct. 1, 1962 to Jan. 1, 1969 and 1945 in the Baltimore area) would yield at least 11 additional exposed fathers and 11 matched fathers, making a total of 72-80 fathers on whom chromosome studies would be carried out. That estimate assumed that the rate of Down's syndrome, ascertainment, and radar exposure would be similar for years to be studied with those years already studied. With the larger current study series available and including those who had worked near radar, it is now estimated that 60 to 70 fathers may be found to be "radar exposed". Thus, with the matched unexposed fathers, the estimated number of persons on whom chromosome studies will be performed has now increased to about 120 to 140. With deaths and refusals, a conservative estimate of 110 to 120 is more plausible.

Significance of this Research

It is important to determine whether the previous interview findings of higher frequencies of military service and radar exposure among fathers of children with Down's syndrome are confirmed by an independent replication of the original study, and by record validation of both the original and current study series. It is also essential to determine whether there is a real difference in military service history between cases and controls other than that which is associated with the increased radar exposure. If the reported associations are confirmed, and a relationship between radar exposure or military service and Down's syndrome in offspring examined and established, the implications would be far reaching. Such associations would suggest that there may be other chromosomal aberrations and other types of genetic defects in offspring, and possibly somatic damage to the exposed fathers. At a time when military and industrial uses of radar and microwaves, and even household exposures to microwaves, are continually expanding, the significance of this problem must not be underestimated. It is pertinent not only to the health of a broad segment of the present population, but as genetic damage, also to that of succeeding generations.

Summary

The project plan thus includes the following:

ORIGINAL SERIES

I. To locate the fathers of cases and controls in the original January 1, 1946 to Obtober 1, 1962 series and bring their records up to date, obtaining more detailed information on military service and radar exposure as well as their experience since our last contact.

II. To obtain from the radar exposed fathers of cases and controls and the unexposed fathers matched to the radar exposed subjects blood samples for chromosome studies and to carry out complete chromosome analysis of these fathers in the original series.

CURRENT SERIES

III. To identify and trace parents of children with Down's syndrome born in the Baltimore area from October 1, 1962 to January 1, 1969 as well as from January 1, 1945 to December 31, 1945 and:

A. Verify diagnoses.

B. Search birth certificates on these affected children.

C. Select controls matched to cases on hospital of birth, date of birth, maternal age, race and sex of infant.

IV. To carry out interviews of parents of Down's cases of current series.

V. To trace the matched controls of the current series and interview their parents.

VI. To validate selected portions of the data obtained by interview against medical records in current series.

VII. To obtain blood samples and carry out chromosome analysis on all fathers reporting radar exposure and on the corresponding fathers of children matched to those whose parents were exposed in the current series.

BOTH SERIES

VIII. To validate paternal military/radar history by independent search of government military files on all fathers irrespective of service/radar report, (as well as carry out chromosome studies indicated above under II and VII respectively).

APPENDIX B

PUBLICATIONS 1 - 5

Reprinted from AMERICAN JOURNAL OF PUBLIC HEALTH, Vol. 53, No. 2, February, 1963

Appendix B
Pub. #1

The authors review epidemiological investigations of mongolism, indicate the unanswered questions that still exist, and point out what they consider fruitful areas for future epidemiological studies of this problem.

SOME EPIDEMIOLOGICAL ASPECTS OF MONGOLISM: A REVIEW

Bernice H. Cohen, Ph.D., M.P.H.; Abraham M. Lilienfeld, M.D., M.P.H., F.A.P.H.A.; and Arnold T. Sigler, M.D.

SINCE 1866 when Langdon-Down first described Mongolism, or Down's Syndrome, numerous epidemiological observations have been made in attempts to determine etiological factors. Less than three years ago Lejeune and co-workers[1] demonstrated the presence of an extra chromosome in cultured connective tissue cells of mongols, thereby strongly suggesting a chromosomal abnormality as the basic defect in this condition. These results have been confirmed by many other workers.[2-4] It is, therefore, desirable at this time to evaluate the past epidemiological observations in the light of these recent cytogenetic findings and to determine the most profitable directions of further epidemiological studies. We shall first discuss briefly the cytogenetic developments, then review the epidemiological studies and finally indicate possible future areas of research. Limitations of space permit only a selective general review rather than an intensive exhaustive one.

Figure 1 presents a photomicrograph of normal human cells.[5] The portion on the left shows chromosomes at metaphase in the dividing cells of a normal human male. On the right these same chromosomes are shown sorted and matched in homologous pairs. In normal adults and children the modal number of chromosomes is 46 or 23 pairs. Each pair has one representative derived from each parent. Of the 23 pairs, 22 are called autosomes and the 23rd pair are the sex chromosomes consisting of an X and Y in the male and 2 X's in the female. The numerical order specified is in accordance with the international standard system of nomenclature adopted at the Denver Conference, 1960.[6]

Figure 2 presents the chromosomes of a mongoloid child.[7] Note that there are 47 chromosomes with an extra member of one of the small acrocentric pairs of autosomes, probably the pair designated as number 21 or 22. This condition in which there is an extra member of a pair is known as trisomy and has been the most frequent chromosomal abnormality found in mongolism. More recently, however, mongols with 46 chromosomes have been reported. In each of these mongols there is at least one aberrant chromosome with a postulated translocation involving an extra portion of the number 21 or 22 chromosome attached to another chromosome. It has been suggested that this unbalanced state, or extra dose of chromatin, is nearly equivalent to that produced in the trisomic condition.[8]

Trisomy is probably the end result of a process called nondisjunction, which is

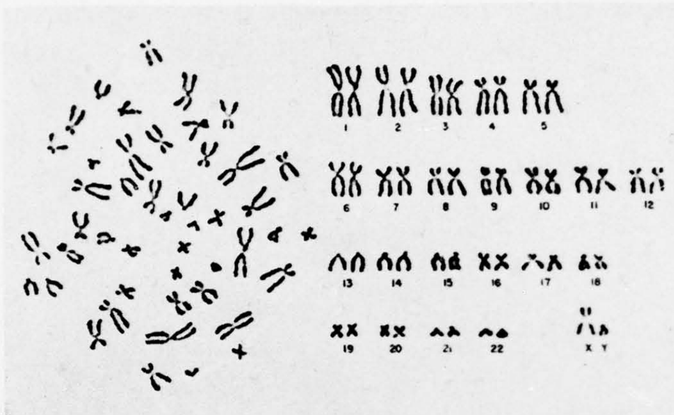


Figure 1—Photomicrograph of Chromosomes at Metaphase in the Dividing Cells of a Normal Human Male. (Courtesy of Barr and Carr, Canadian Medical Association Journal.[5])

the failure of members of a chromosome pair to separate and which most likely occurs at the first or second meiotic division in the formation of either the ovum or sperm. Less likely, although theoretically possible, the nondisjunction might take place at the gonial stage of the gamete or at the first cleavage division of the fertilized ovum or zygote.

Figure 3 illustrates diagrammatically the difference between a normal and a nondisjunctional division.[6] The upper

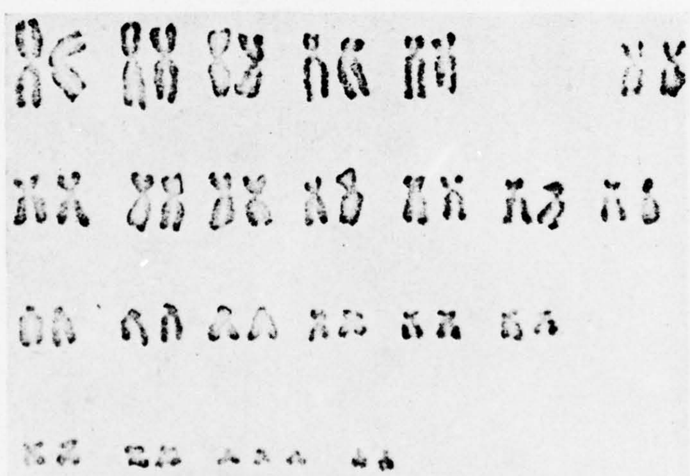


Figure 2—Chromosomes of a Mongoloid Child. Note that there are 47 chromosomes with an extra small acrocentric chromosome. (Courtesy of Hirschhorn and Cooper, American Journal of Medicine.[7])

portion of this diagram shows the orientation of the chromosomes on the equatorial plate followed by separation of members of the chromosome pairs so that each daughter cell has an equal number of chromosomes. In the lower portion, one member of the pair does not separate from its partner; and consequently, one daughter cell has an extra chromosome representative while the other is deficient with respect to that one chromosome. When a gamete (ovum or sperm) carrying the extra chromosome is fertilized by, or fertilizes a normal gamete from the other parent, the resultant embryo, if viable, is trisomic.

Nondisjunction leading to trisomy, and chromosomal breaks resulting in translocations, have been demonstrated in a wide range of organisms, including maize, Drosophila, the house mouse and man[1,9-14] and in both sexes as well.[11,13-15,17-18] Nondisjunction and other chromosomal abnormalities in behavior and structure have been produced by such agents as ionizing radiation, Co_2, and ammonia vapor.[10-14,16-27] There is evidence that specific genes may also affect the frequency of nondisjunction.[11] In addition, interactions between agents have been shown to have an effect. For example, oxygen and cyanide influence the effect of radiation on the frequency of nondisjunction,[10,25,26] and in Drosophila, aging of the females enhances both radiation- and Co_2-induced effects.[24,27]

These cytogenetic findings strongly suggest that, if there are any environmental factors producing the sequence of events leading to the chromosomal defects in mongolism, they must be acting on parental gametes or on the fertilized ovum not later than several days after fertilization. This timing of events has a bearing on the evaluation of various hypotheses and on the selection of areas for further investigation.

The incidence of mongolism has been estimated by numerous investigators. These are summarized in Table 1.[28-42] The periods of study extend as far back as 1923 and are as recent as the late

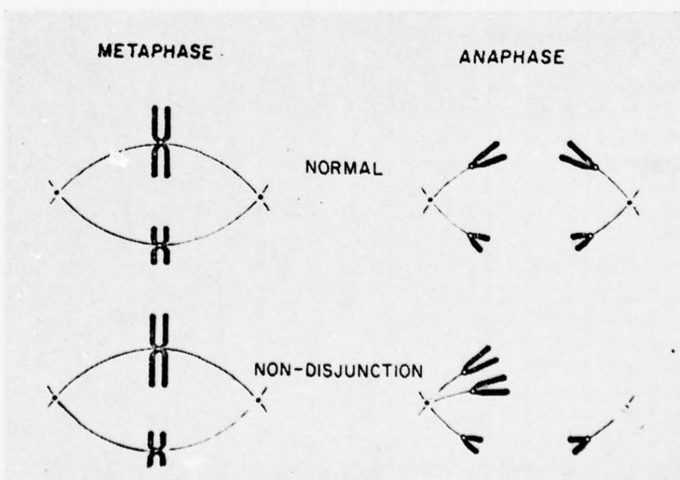


Figure 3—Diagrammatic Representation of a Normal and a Nondisjunctional Division. (Modified by permission of Sohval, American Journal of Medicine.[6])

Table 1—Summary of Estimates of Incidence Rates of Mongolism

Investigator	Ref. No.	No. of Mongols	Population No. Type	Incidence Frequency	Per 1,000	Time Period of Study	Source of Data
Jenkins (1933)	28	6	3,818*	1/636	1.57	1926-31 incl.	United States—Chicago Presbyterian Hospital
Malpas (1937)	29	18	13,964‡	1/776	1.29	1923-32	Great Britain—Liverpool Maternity Hospital
Keller (1938)	30	23	11,000‡	1/478	2.9	About 10 yrs	
Beidleman (1945)	31	48	14,000‡	1/292	3.42	1931-41	United States—Boston Lying-In Hospital
Landtmann (1948)	32	4	3,593‡	1/898	1.11	1945-48	England—University College Hospital, London
Stevenson, Worcester, and Rice (1950)	33	15	29,024† incl. 787 stillbirths	1/1935	0.5	1930-41	United States—Boston Lying-In Hospital
Parker (1950)	34	32	27,931*	1/873	1.15	Jan. 1 '39-Dec. 31 '48	United States—Gallinger Municipal Hospital, Washington, D. C.
		3 W	2,905*	1/968	1.03		
		29 N	25,026*	1/863	1.16		
Hug (1951)	35	130	67,645‡	1/520	1.92	1930-1949	Switzerland—Zurich
		99	49,218‡	1/497	2.01		St. Gallen
		31	18,427‡	1/594	1.68		
Carter and MacCarthy (1951)	36	100	66,366†	1/666	1.51	1943-1948	England—10 hospitals in London
Øster (1953)	37	52	39,788*	1/765	1.31	1938-1948	Denmark—University Hospital, Copenhagen
Harris and Steinberg (1954)	38	11	8,716*	1/792	1.26	Jan. 1, 1944-Dec. 31, 1950	United States—St. Mary's Hospital, Rochester, Minn.
McIntosh, Merritt, Richards, Samuels, and Bellows (1954)	39	11	5,964**	1/542	1.84	Oct. 1946-March 1952	United States—Sloane Hospital for Women, New York City
Record and Smith (1955)	40	252	231,619†	1/919	1.09	1942-1952	England—City of Birmingham residents
Pleydell (1957)	41	86	52,729†	1/613	1.63	1944-1955 incl.	England—Entire County of Northamptonshire
		84	52,727*	1/628	1.59		
Collman and Stoller (1961)	42			1/688	1.45		Australia—Survey

* Live births
† Total births—(live and stillbirths)
‡ Births and/or maternities (not specified whether live and/or stillborn)
** Pregnancies including abortions and stillbirths
W = white
N = Negro

McIntosh, Merritt, Richards, Samuels, and Bellows (1954)	39	11	5,964**	1/542	1.84	Oct. 1946-March 1952	United States—Sloane Hospital for Women, New York City
Record and Smith (1955)	40	252	231,619†	1/919	1.09	1942-1952	England—City of Birmingham residents
Pleydell (1957)	41	86	52,729†	1/613	1.63	1944-1955	England—Entire County of Northamptonshire
		84	52,727*	1/628	1.59	incl.	
Collman and Stoller (1961)	42			1/688	1.45		Australia—Survey

* Live births
† Total births—(live and stillbirths)
‡ Births and/or maternities (not specified whether live and/or stillborn)
** Pregnancies including abortions and stillbirths
W = white
N = Negro

fifties. They encompass spans of observation as brief as six years and as long as 20 years. Though the range of incidence rates extend from 0.5 per 1,000 births to 3.4 per 1,000, 11 of the 15 studies present estimates of between 1/500 and 1/900 births. This is surprisingly consistent when the geographical and temporal range as well as variability in diagnostic criteria and method of ascertainment are considered. On the other hand, the fact that the two most extreme estimates, those of Beidleman[31] and Stevenson, et al.,[33] were derived from records in the same hospital in an overlapping time period raises many questions.

Of particular interest are Parker's estimates for Negroes and whites at Gallinger Municipal Hospital in Washington.[34] The similarity of the incidence values for whites, 1/968, and for Negroes, 1/863, with one another, as well as that of the Negro estimate with the over-all range of Caucasian values should lead one to question the opinion that mongolism is less common among non-Caucasians. Nevertheless, this represents only a single study sample; and it is possible that the number of cases was not adequate to detect a difference between Negroes and Caucasians, if one truly existed.

It would also be of interest to know whether the incidence of mongolism has changed over time, since if radiation exposure of parents is a major factor in producing chromosomal aberrations, one would expect an increase in incidence rates with increasing exposure of the population to medical radiation.[43-45] It is difficult to evaluate reported incidence rates because of the variability in methods used to estimate them in the different studies and because of the fact that in most studies only crude rates are available. Since there is an association between increasing maternal age and the incidence of mongolism, as will be discussed, the comparison of crude incidence rates leaves much to be desired. Better estimates of incidence rates are needed

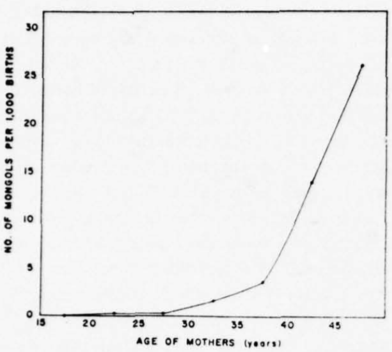


Figure 4—Incidence Rates of Mongolism by Maternal Age. (Rates from Carter and MacCarthy.[36])

for comparative purposes and as a base line for future studies.

Sex Ratio

There has been much conflicting evidence regarding the sex ratio in mongolism. An excess of males was indicated by some investigators and this view had been generally held. More recently, these findings have been criticized because many of the studies were based on institutionalized populations and possibly female mongols are more likely to be kept at home than male mongols. The sex ratio at birth should provide the most satisfactory estimate. On the basis of statistics available at this time, there is certainly no reliable evidence of an aberrant sex ratio in mongolism.[31,34,35,37,40]

Maternal and Paternal Ages and Birth Order

The most striking relationship that has been observed with respect to mongolism is the increasing incidence rate with advancing maternal age. This has been regularly reported in all studies.[8,28,36,37,46] Figure 4 illustrates this relationship with data collected by Carter and MacCarthy from ten hospitals in London and environs. Mothers over 45 years of age have about 100 times the risk of giving birth to a mongol child than do mothers in their twenties. Jenkins,[28] in a further analysis of these maternal age incidence rates, plotted them on logarithmic paper with interesting results. The same data of Carter and MacCarthy shown in Figure 4 are so plotted in Figure 5. We note that up to age 30 the incidence rate does not change with age, but that after 30 years of age the rates are represented by a straight line. This separation of the incidence rates into two components in this manner suggests that there may be two types of mongolism, one that is age dependent and one that is not age dependent. Such a possibility is consistent with other types of data. Recently, Penrose[8] has collected the cases of mongolism associated with chromosomal translocation and found a preponderance of younger mothers. Of additional interest are the reports of ages of mothers of children with trisomy other than that associated with mongolism, indicating in a very limited sample that the maternal ages are on the whole in the older age range.[47] Thus it is postulated that trisomy may be age dependent, and translocation age inde-

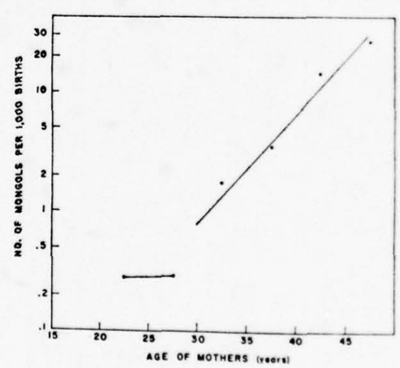


Figure 5—Incidence Rates of Mongolism by Maternal Age. (Rates from Carter and MacCarthy.[36])

pendent. Such a dichotomy in the etiology of mongolism is further suggested by the reported difference in androgyny scores[48] and steroid excretion levels[49] between younger mothers and older mothers of mongols. As yet, these observations can be considered only in the realm of "clinical impressions" and must await further validation.

Mongolism also has been found to be associated with the age of the father at the birth of the affected child, although this relationship is not so marked as that with maternal age. Since maternal and paternal ages are themselves highly correlated, it is of interest to determine whether the association is primarily with one or the other, or both. Penrose[50] has analyzed some data and interpreted them as indicating that the principal relationship is with maternal age and that the paternal age association is a secondary one. A review of these analyses and those of Jenkins[28] suggests that the issue is still unsettled and there is a need for further investigation with adequate control groups. This point is of some relevance with respect to further research orientation. In general, investigators have interpreted the maternal age effect to indicate that, in looking for factors which influence mongolism, one should study maternal factors rather than paternal factors. However, we feel that a possible paternal influence has not been completely eliminated on the basis of available evidence.

Another problem concerns the increase in frequency of mongolism with increasing birth order. This appears to result from the strong association of maternal age with birth order; and apparently, birth order has no independent effect.[51,52]

Maternal Constitutional and Prenatal Factors

Stimulated by the marked association of mongolism with maternal age, there has been much interest in the role of maternal health, reproductive, hormonal and constitutional factors, as well as prenatal events, in the frequency of mongolism. Some studies have reported that mothers of mongols tend to have an earlier age at menarche and later age of menopause as well as an excessively long interval between the birth of the mongol and the previous pregnancy.[28,37,48] There are conflicting reports concerning a higher frequency of miscarriages prior to the birth of the mongol.[31,37,48] It is difficult to evaluate these reports since many have been uncontrolled or inadequately controlled. A study by Lunn[53] indicated that mothers of mongols did not have a larger percentage of abortions prior to the mongol birth than a control group matched by maternal age. However, this was an investigation of 117 mongol children, a number that might be inadequate to detect any but a marked difference.

Several studies have reported a relatively high frequency of maternal complications during the mongol pregnancy, including gestational hemorrhage, threatened abortion, and uterine disorders.[31,54] These findings as well as those of an accumulation of illnesses and intercurrent infections around the time of conception and during the mongol pregnancy must now be interpreted in the light of the recent cytogenetic observations.[37,48,54] Many of these prenatal complications occurred after the time period when they could have produced the type of direct effect necessary for the chromosomal abnormality of mongols. Therefore, these pregnancy difficulties may merely reflect the older maternal ages; or they may be a result of, rather than a cause of, the mongol pregnancy.

In addition to the ovarian hormones, other endocrine factors have been suggested as possible etiological factors. There is conflicting evidence on the frequency of maternal thyroid abnormalities for which some investigators report a high incidence.[37,48,49,55-57] Such a find-

Table 2—Chromosome Analysis of Families of Mongol Index Cases

Classification	Ref. No.	Mongol Index Case	Cytogenetic Category	Maternal Age	Other Relatives with Abnormalities
1. Familial Mongolism with Familial Chromosome Aberration	63	M (46T) F (46T)	Translocation 13–15:21–22	23	Mother, maternal grandmother and normal F sib with (45T)
	64	M (46T)	Translocation 13–15:21–22	23	Mother (45T) Maternal grandmother (45T) 1 male mongol sib 1 male mongol first cousin
	65	M (46T)	"	32	Mother (45T) 2 mongol male sibs dead 1 "normal" *female sib dead of* leukemia
	66	M (46T)	Translocation 15:21	22	Mother, maternal aunt, maternal grandmother, one male mongol sib dead, one male mongol cousin — all (45T)
	66	F (dead)	?	20	Mother (45T) 21/22:21/22; one male mongol sib dead in infancy
	66	M mosaic	Trisomic 21/tetrasomic 21 mosaic	21	Father normal/tetrasomic 21 mosaic; one female mongol sib dead
	67	F 47 M 47	Trisomy 21/22 Trisomy 21/22	23	Mother translocation 13–15/21
	68	M (46T)	Translocation 13–15/21	27*	2 mongol female sibs 1 mongol maternal aunt
	69	F	Translocation 15:21	?	Mother 15/21 translocation, 1 male mongol sib dead
	69	F 46	Translocation type?		Father 45 chromosomes with translocation 2 mongol sibs dead
2. Familial Chromosome Aberration	70	F (46T)	Translocation	31	Mother (45T)
	71	M (46T)	"	24	Mother (45T)
	72	M (46T)	"	28	Mother (45T)
	73	M (46T) with leukemia	" ?	29	Mother abnormal karyotype with translocation 14?, 1 minute chromosome in "normal" male sib (45)
	74	M (46T)	Translocation 21/22:21/22	39	Father 47 chromosomes trisomic—19?
	8	M (46T)	Translocation 21/22:21/22 (extra metacentric fragment)	33	Parents not available ?
	8	M (46T)	Translocation 21/22:21/22	39	Parents not available ?

* = age at birth of first mongol
s = trisomy
T = Translocation
M = Male
F = Female
? = Unknown condition

Classi-fication	Ref. No.	Mong[...] Index C[...]
3. Familial Mongolism	66	F 47s
	66	M 47s
	66	M 47
	66	M 47s
	66	M 47s
	66	M dead
	75	M 47

* = age at birth of first mong[...]
s = trisomy
T = Translocation

ing, if confirmed, wou[...]
ticular interest since the[...]
genetic evidence *that*[...]
increase "stickiness" of t[...]
and thus influence nondi[...]
ternal diabetes mellitus a[...]
abnormalities have al[...]
gested.[48,49,57] In a stud[...]
as an index of maternal [...]
adrenal function, no d[...]
found between mothers [...]
mothers of controls; bu[...]
already indicated, a sign[...]
mean androgyny scor[...]
mothers of mongols, i.e., [...]
as compared to older on[...]

Familial Studies

While the importan[...]
studies to determine [...]
factors in mongolism an[...]
basis for genetic couns[...]
of mongol children has [...]
ognized, the cytogenet[...]
have added another dir[...]
studies.

Table 2—(Continued)

Classification	Ref. No.	Mongol Index Case	Cytogenetic Category	Maternal Age	Other Relatives with Abnormalities
3. Familial Mongolism	66	F 47s	Trisomic—21	20	Parents normal; 1 female mongol sib dead in infancy
	66	M 47s	Trisomic—21	33*	Parents normal; 1 male mongol sib dead in infancy
	66	M 47	" —21	38*	Parents normal; 1 F mongol sib dead in infancy
	66	M 47s	" —21	45*	Parents normal; 1 F mongol sib dead at 6 mos
	66	M 47s	" —21	29	Parents normal; 1 F mongol sib dead at 7 yrs
	66	M dead	? ?	20*	Parents normal; 1 M mongol sib (Trisomic—21)
	75	M 47	Trisomy	25*	One mongol sib dead

* = age at birth of first mongol
s = trisomy
T = Translocation

M = Male
F = Female
? = Unknown condition

ing, if confirmed, would be of particular interest since there is some cytogenetic evidence that thyroxin may increase "stickiness" of the chromosomes and thus influence nondisjunction.[58] Maternal diabetes mellitus as well as adrenal abnormalities have also been suggested.[48,49,57] In a study of body build as an index of maternal constitution and adrenal function, no differences were found between mothers of mongols and mothers of controls; but there was, as already indicated, a significantly higher mean androgyny score in younger mothers of mongols, i.e., under 27 years, as compared to older ones.

Familial Studies

While the importance of familial studies to determine possible genetic factors in mongolism and to serve as a basis for genetic counseling of parents of mongol children has long been recognized, the cytogenetic observations have added another dimension to such studies.

Results of earlier investigations of familial aggregation were contradictory in that some investigators observed no unusual familial concentration of mongols, whereas others did.[8,37,59,60] This led to the study of the possible familial aggregation of "micro symptoms" of mongolism, such as, fissured tongue, transverse palmar crease, and the position of the palmar triradii.[8,61,62] Even though an excess frequency of such micro symptoms was reported among normal family members of mongols, interpretation of these results is difficult.

Many of the recent family studies of mongolism have included chromosomal analyses of individual families. A collection from the recent literature is summarized in Table 2[8,63-75] which includes: (1) cases of familial mongolism with familial translocation or other aberrations[63-69]; (2) familial translocation or other chromosome aberration, with index mongol as the only diagnosed mongol in the family[8,70-74]; and (3) familial mongolism with no other observed chromosomal abnormalities in family mem-

bers.[66,75] These reports have suggested familial aggregation of certain chromosomal abnormalities, particularly translocation. Of considerable interest are several observations of such translocation in family members who are clinically normal. It has been suggested further that, as in other organisms,[10,17,18] the presence of one type of chromosomal abnormality in a parent may influence the occurrence of another type, such as the one leading to mongolism.[67,74]

Most recently Carter and Evans[76] concluded from their survey of families of 642 mongols that mothers of mongol children have a higher than expected risk of having a second mongol child. Interestingly enough, younger mothers had a greater excess risk than older mothers. Chromosome studies of the families with more than one mongol child in this series of cases revealed chromosomal abnormalities in nonmongol family members of three of the nine families with multiple mongols.[66] At present, these findings on familial aggregation must be considered only suggestive since unknown biases may have been introduced in the selection of cases or even groups examined.

Twin studies, too, have suffered from similar methodological problems.[37,77] Recently Allen and Baroff,[78] cognizant of such difficulties, attempted a systematic investigation of a consecutive series of twins admitted to the New York State schools. They concluded that almost 100 per cent of monozygotic twins are concordant with respect to mongolism as compared to about 4 per cent of dizygotic twins. These results are in agreement with the cytogenetic expectancy. Also strikingly consistent with genetic expectancy is the observation of four mongols among the eight offspring of mongol females reported to have reproduced.[8]

Relationship with Leukemia and Ionizing Radiation

Since Ingalls[79] first demonstrated the simultaneous occurrence of mongolism and leukemia, there have been many case reports, and a few systematic studies indicating that mongols have an increased risk of incurring leukemia.[73,80-84] Wald[85] and co-workers reviewed all the death certificates in Pennsylvania during 1955-1959 and observed that the incidence of leukemia in mongols was significantly higher than that found in the general population. In England, Holland and co-workers[86] found the mortality from leukemia among patients with Down's syndrome to be 20 times greater than expectancy. Moreover, it is of interest that leukocytes of many mongols have an unusual morphological pattern: i.e., polymorphonuclear neutrophils with fewer lobes than found in the general population.[87] These findings are especially interesting as a result of recent observations of chromosomal aberrations in individuals with leukemia. For example, Jacobs[89] reported the presence of a small partially deleted chromosome (called the Philadelphia Chromosome[90-93]) in 14 untreated cases of chronic myeloid leukemia. The abnormal chromosome is thought to be number 21, the same one involved in mongolism. The relevance of this finding is uncertain since the leukemia observed in mongols is usually of the acute variety and none of the subjects with mongolism and acute leukemia who have been studied thus far have the chromosome abnormality observed in chronic leukemia.[94]

In view of the known biological relationship of leukemia to ionizing radiation and the experimental studies of the relationship of ionizing radiation to chromosomal aberrations,[10,16-26,43-45] it is of interest to determine whether parents of mongol children have had excessive exposure to radiation. The results of two studies have been reported. Lunn,[53] in the study mentioned earlier, determined that the per cent of significant histories of x-ray exposure of mothers of mongols was no different from that of mothers of controls. More recently, Uchida[88] reported that 28 per cent of mothers of mongols were exposed to four or more

abdominal x-rays or
pared to 4 per cent o
children and 14 pe
There are several n
with both studies, so
still be considered an
ject for further inves
Nevertheless, this
ships is provocative
Figure 6 along with
cussed. The dotted
ciations based on a
quiring confirmation
The solid lines indica
on several reports a
would judge as bein
dence. Where arrow
lines, direction of
gested; otherwise no
ship is postulated.

General Comments

Though these asso
as to the etiological

Figure 6—Schemati
Demonstrated Ass

abdominal x-rays or fluoroscopy as compared to 4 per cent of mothers of cleft lip children and 14 per cent of neighbors. There are several methodological faults with both studies, so that the issue must still be considered an open one and a subject for further investigation.

Nevertheless, this pattern of relationships is provocative and is illustrated in Figure 6 along with others already discussed. The dotted lines indicate associations based on a single report or requiring confirmation for other reasons. The solid lines indicate associations based on several reports and/or on what one would judge as being more reliable evidence. Where arrowheads are placed on lines, direction of association is suggested; otherwise no cause-effect relationship is postulated.

General Comments

Though these associations provide clues as to the etiological factors in mongolism, some, especially those of radiation with mongolism as well as of chromosomal aberrations with leukemia, need further *documentation and clarification.* As the hypothesized pattern stands now, it falls short of a cause and effect relationship. Theories consistent with the observations can merely postulate the missing steps, but further cytogenetic and epidemiological evidence is needed for their validation.

The observations made during the past two to three years appear to have brought us closer to elucidating the cause of mongolism.[95] Yet, interesting as the results of the cytogenetic investigations may be, it should be emphasized that cytogenetics is a very complex field with numerous technical difficulties. In addition, the *sampling of individuals and families for* cytogenetic examination has been so irregular that extrapolation of the results to any discernible affected group of population segment is not possible at this time. Hopefully, many of these problems will be resolved in the near future.

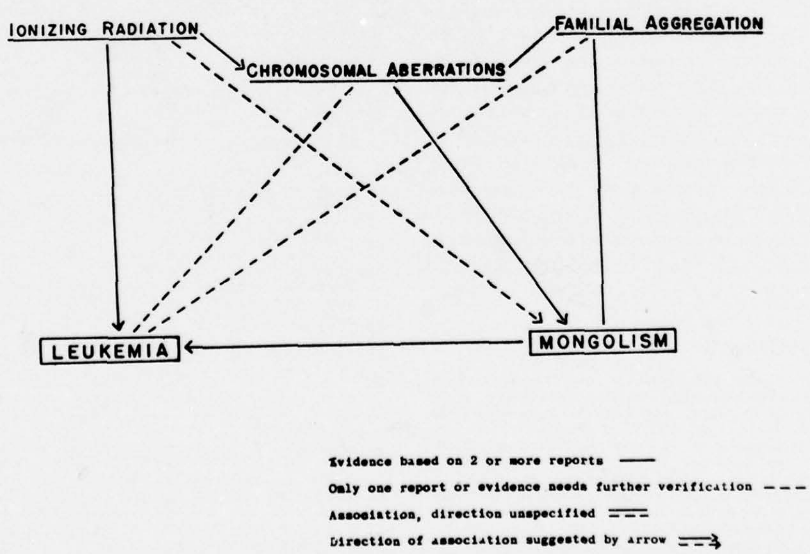


Figure 6—Schematic Diagram Illustrating Epidemiologically and/or Experimentally Demonstrated Associations of Mongolism with other Conditions.

Field epidemiological studies can assist in the evaluation of these findings. A cytogenetic investigation of a sample of the general population would be invaluable in establishing more definitive base lines for chromosomal constitution in phenotypically normal individuals. These also would help in evaluating the significance of findings in those with clinically diagnosed abnormalities and in determining the factors that may be producing these abnormalities.

The following types of studies, one of which we are initiating, are now indicated: (1) a well controlled investigation of parental radiation, reproductive, medical, and drug history; (2) a study of family patterns of mortality and morbidity in all classes of cases and controls; (3) a study of the chromosomal constitution of cases, controls, and their immediate family members; and (4) a study of histologic and histochemical changes of the ovaries and fallopian tubes occurring with age to learn whether these changes might provide an explanation for the increased incidence of mongolism with maternal age. For the epidemiologist, here is an unequaled opportunity to explore the possible contributions that epidemiologic studies might make in determining factors that may have an influence on the genetic constitution of individuals. In view of the increasing recognition of genetically determined human diseases, epidemiologists will doubtless be faced with many similar situations in the future.

REFERENCES

1. Lejeune, J.; Gautier, M.; and Turpin, R. Etudes des chromosomes somatiques de neuf enfants mongoliens. Comp. rend. Acad. Sc. Paris 248:1721–1722, 1959.
2. Jacobs, P. A.; Baikie, A. G.; Court-Brown, W. M.; and Strong, J. A. The Somatic Chromosomes in Mongolism. Lancet 1:710 (Apr.), 1959.
3. Böök, J. A.; Fraccaro, M.; and Lindsten, J. Cytogenetical Observations in Mongolism. Acta paediat. Upps. 48:453–468 (Sept.), 1959.
4. a. Ferguson-Smith and Levan. Unpublished.
   b. Ferguson-Smith, M. Cytogenetics in Man. A.M.A. Arch. Int. Med. 105:627–639 (Apr.), 1960.
5. Barr, M. L., and Carr, D. H. Sex Chromatin, Sex Chromosomes and Sex Anomalies. Canad. M. A. J. 83:979–986, 1960.
6. Sohval, A. R. Recent Progress in Human Chromosome Analysis and Its Relation to Sex Chromatin. Am. J. Med. 31,3:397–441 (Sept.), 1961.
7. Hirschhorn, K., and Cooper, H. L. Chromosomal Aberrations in Human Disease. A Review of the Status of Cytogenetics in Medicine. Ibid. 31,3:442–470 (Sept.), 1961.
8. Penrose, L. S. Mongolism. Brit. M. Bull. 17,3:184–189 (Sept.), 1961.
9. Saffir, S. R. Genetic and Cytological Examination of the Phenomena of Primary Non-disjunction in Drosophila melanogaster. Genetics 5:459–487, 1920.
10. Swanson, C. P. Cytology and Cytogenetics. Englewood Cliffs, N. J.: Prentice-Hall, 1957.
11. Morgan, T. H.; Bridges, C. B.; and Sturtevant, A. H. The Genetics of Drosophila. Bibliogr. Genetica II: 3–262, 1925.
12. Waddington, C. H. An Introduction to Modern Genetics. London, England: Allen & Unwin, 1956.
13. a. Stern, C. On the Occurrence of Translocations and Autosomal Non-disjunction in Drosophila melanogaster. Proc. Nat. Acad. Sc. 20:36–39, 1934.
    b. ————. Principles of Human Genetics (2nd ed.). San Francisco, Calif.: W. H. Freeman, 1960.
14. a. Demerec, M., and Farrow, J. G. Non-disjunction of the X-chromosome in Drosophila virilis. Proc. Nat. Acad. Sc. 16:707–710, 1930.
    b. ————. Relation Between the X-ray Dosage and the Frequency of Primary Non-disjunctions of X-chromosomes in Drosophila virilis. Ibid. 16:711–714, 1930.
15. Russell, E. L.; Russell, L. B.; and Gower, J. S. Exceptional Inheritance of a Sex-linked Gene in the Mouse Explained on the Basis that the X/O Sex-chromosome Constitution Is Female. Ibid. 45:554–560, 1959.
16. Gooch, P. C. Induced and Spontaneous Chromosome Aberrations in Human Leukocytes Irradiated in vivo and in vitro. Presented at Blood-Bone Marrow Tissue Culture and Cell Separation Conference, National Institutes of Health, Bethesda, Md., October 20, 1961.
17. Glass, B. A Comparative Study of Induced Mutation in the Oocytes and Spermatozoa of Drosophila melanogaster I. Translocations and Inversions. Genetics 40,2:252–267 (Mar.), 1955.
18. Frost, J. N. Autosomal Non-disjunction in Males of Drosophila melanogaster. Genetics 46,1:40–54 (Jan.), 1961.
19. Mavor, J. W. The Production of Non-disjunction by X-rays. Science 55:295–297, 1922.
20. Anderson, E. G. The Constitution of Primary Exceptions Obtained after X-ray Treatment of Drosophila. Genetics 16:386–396, 1931.
21. Hollander, A. Radiation Biology (Vol. I, Part I). New York, N. Y.: McGraw-Hill, 1954.
22. Bender, M., and Wolff, S. X-ray Induced Chromosome Aberrations and Reproductive Death in Mammalian Cells. Am. Naturalist XCV, 880:39–52, 1961.
23. Puck, T. T. The Action of Radiation on Mammalian Cells. Ibid. XCIV, 874:95–109 (Jan.-Feb.), 1960.
24. Patterson, J. T.; Brewster, W.; and Winchester, A. M. Effects Produced by Aging and X-raying Eggs of Drosophila melanogaster. J. Hered. 23:325–333, 1932.
25. Abrahamson, S. The Influence of Oxygen on the X-ray Induction of Structural Changes in Drosophila Oocytes. Genetics 44:173–185, 1959.
26. Savhagen, R. The Effect of Oxygen Concentration on the Frequency of Induced XO Males and Nondisjunction Females after Irradiation of Drosophila Males. Hereditas 47,2:163–189, 1961.
27. Mottram, J. C. The Effect of Carbon Dioxide on the Occurrence of Non-disjunction in Drosophila. J. Exper. Biol. 7:370–372, 1930.

28. Jenkins, R. L. Etiology
Child. 45:506–519, 1933.
29. Malpas, P. The Incidence
and the Significance of
Environment in Their Cau
44:434–454, 1937.
30. Keller, J. Zur Kenntnis
besonderer Berucksichtegan
Diss. Zurich, 1958 (after
31. Beidleman, B. Mongolism:
cluding an Analysis of
Records of the Boston
Ment. Deficiency 50:35–53,
32. Landtman, B. On the Rel
Conditions During Pregna
formations. Arch. Dis. Ch
33. Stevenson, S. S.; Worce
677 Congenitally Malform
Gestational Characteristics
tions. Pediatrics 6:37–50,
34. Parker, G. F. The Inci
becility in the Newborn
494, 1950.
35. Hug, E. Das Geschlectsver
Ann. paediat. 177:31–54 (J
36. Carter, C., and MacCarthy
golism and Its Diagnosis
Social Med. 5:83–90, 1951.
37. Oster, J. Mongolism. A
gation Comprising 526 M
and Neighboring Isiands
Danish Science Press., Ltd
38. Harris, L. E., and Stein
Observed During the First
Live-born Infants. Pediat
1954.
39. McIntosh, R.; Merritt, K
Samuels, M. H.; and Bell
of Congenital Malformati
Pregnancies. Ibid. 4,5:505–
40. Record, R. G., and Smith,
and Sex Distribution of
Prev. & Social Med. 9:10–
41. Pleydell, M. J. Mongolism
ties. An Epidemiological S
Lancet 1:1314–1319 (June
42. Collman, R. D., and S
Mongoloid Births in Vict
A.J.P.H. 52:813–829 (May),
43. Tough, I. M.; Buckton, K
Court-Brown, W. M. X-r
Damage in Man. Lancet II
44. Boyd, E.; Buchanan, W.
age to Chromosomes by Th
iodine. Ibid. 1:977–978 (M
45. Stewart, J. S. S., and S
somal Aberration after Diag
1:978–979 (May 6), 1961.
46. a. Penrose, L. S. Maternal
golism. J. Ment. Sc. 97
b. ————. Mongolian
Maternal Age. Ann. New
502, 1953-1954.
47. Smith, D. W.; Patau, K.;
somal Trisomy Syndromes.
22), 1961.
48. Coppen, A., and Cowie,
Mongolism. Brit. M. J. 1:1
49. Rundle, A.; Coppen, A.;
Excretion in Mothers of M
(Oct. 14), 1961.
50. Penrose, L. S. The Relative
Maternal Age in Mongolism
225, 1933.
51. a. Penrose, L. S. The
portance of Birth Order
Mongolism. Proc. Roy.
450, 1934.

28. Jenkins, R. L. Etiology of Mongolism. Am. J. Dis. Child. 45:506-519, 1933.
29. Malpas, P. The Incidence of Human Malformation and the Significance of Changes in the Maternal Environment in Their Causation. J. Obst. & Gynaec. 44:434-454, 1937.
30. Keller, J. Zur Kenntnis des Mongolismus unter besonderer Beruckaichtegang der Aetiologie, Inaugur Diss. Zurich, 1958 (after Oster, 1953).
31. Beidleman, B. Mongolism: A Selective Review Including an Analysis of Forty-two Cases from the Records of the Boston Lying-In Hospital. Am. J. Ment. Deficiency 50:35-53, 1945.
32. Landtman, B. On the Relationship Between Maternal Conditions During Pregnancy and Congenital Malformations. Arch. Dis. Childhood 23:237-246, 1948.
33. Stevenson, S. S.; Worcester, J.; and Rice, R. G. 677 Congenitally Malformed Infants and Associated Gestational Characteristics. I. General Considerations. Pediatrics 6:37-50, 1950.
34. Parker, G. F. The Incidence of Mongoloid Imbecility in the Newborn Infant. J. Pediat. 36:493-494, 1950.
35. Hug, E. Das Geschlectsverhaltnis beim Mongolismus. Ann. paediat. 177:31-54 (July), 1951.
36. Carter, C., and MacCarthy, D. Incidence of Mongolism and Its Diagnosis in the Newborn. Brit. J. Social Med. 5:83-90, 1951.
37. Oster, J. Mongolism. A Clincogenealogical Investigation Comprising 526 Mongols Living in Seeland and Neighboring Islands in Denmark. Copenhagen: Danish Science Press., Ltd., 1953.
38. Harris, L. E., and Steinberg, A. G. Abnormalities Observed During the First Days of Life in 8,716 Live-born Infants. Pediatrics 14,4:314-326 (Oct.), 1954.
39. McIntosh, R.; Merritt, K. K.; Richards, M. R.; Samuels, M. H.; and Bellows, M. T. The Incidence of Congenital Malformations: A Study of 5,964 Pregnancies. Ibid. 4,5:505-522 (Nov.), 1954.
40. Record, R. G., and Smith, A. Incidence, Mortality, and Sex Distribution of Mental Defectives. Brit. J. Prev. & Social Med. 9:10-15, 1955.
41. Pleydell, M. J. Mongolism and Congenital Abnormalities. An Epidemiological Study in Northamptonshire. Lancet 1:1314-1319 (June 29), 1957.
42. Collman, R. D., and Stoller, A. A Survey of Mongoloid Births in Victoria, Australia, 1942-1957. A.J.P.H. 52:813-829 (May), 1962.
43. Tough, I. M.; Buckton, K. E.; Baikie, A. J.; and Court-Brown, W. M. X-ray Induced Chromosome Damage in Man. Lancet II:849-851 (Oct. 15), 1960.
44. Boyd, E.; Buchanan, W. W.; and Lennox, B. Damage to Chromosomes by Therapeutic Doses of Radioiodine. Ibid. 1:977-978 (May 6), 1961.
45. Stewart, J. S. S., and Sanderson, A. R. Chromosomal Aberration after Diagnostic X-irradiation. Ibid. 1:978-979 (May 6), 1961.
46. a. Penrose, L. S. Maternal Age in Familial Mongolism. J. Ment. Sc. 97:738-747 (Oct.), 1951.
b. ———. Mongolian Idiocy (Mongolism) and Maternal Age. Ann. New York Acad. Sc. 57:494-502, 1953-1954.
47. Smith, D. W.; Patau, K.; and Therman, E. Autosomal Trisomy Syndromes. Lancet II:211-212 (July 22), 1961.
48. Coppen, A., and Cowie, V. Maternal Health and Mongolism. Brit. M. J. 1:1843-1847 (June 18), 1960.
49. Rundle, A.; Coppen, A.; and Cowie, V. Steroid Excretion in Mothers of Mongols. Lancet II:846-848 (Oct. 14), 1961.
50. Penrose, L. S. The Relative Effects of Paternal and Maternal Age in Mongolism. J. Genetics 27,2:219-225, 1933.
51. a. Penrose, L. S. The Relative Aetiological Importance of Birth Order and Maternal Age in Mongolism. Proc. Roy. Soc. Lond. s.B. 115:431-450, 1934.
b. ———. A Method of Separating the Relative Aetiological Effects of Birth Order and Maternal Age, with Special Reference to Mongolian Imbecility. Ann. Eugenics 6:108-122+, 1944-1945.
52. Smith, A., and Record, R. G. Maternal Age and Birth Rank in the Aetiology of Mongolism. Brit. J. Prev. & Social Med. 9:51-55, 1955.
53. Lunn, J. E. A Survey of Mongol Children in Glasgow. Scottish M. J. 4:368-372, 1959.
54. Ingalls, T. H. Etiology of Mongolism. Epidemiologic and Teratologic Implications. Am. J. Dis. Child. 74:147-165, 1947.
55. Benda, C. E. Mongolism and Cretinism. New York, N. Y.: Grune and Stratton, 1946.
56. ———. Prenatal Maternal Factors in Pregnancy. J.A.M.A. 139:979-985 (Apr. 9), 1949.
57. Kratter, F. E. Endocrine Factors in the Aetiology of Mongolism. J. Ment. Sc. 106,445:1405-1407 (Oct.), 1960.
58. Ferguson-Smith, M. Personal communication.
59. Penrose, L. S. A Clinical and Genetic Study of 1280 Cases of Mental Defect. Med. Res. Council Spec. Rep. Ser. No. 229. London, England: His Majesty's Stationery Office, 1938.
60. Engler, M. Mongolism (Peristatic amentia). Bristol, England: John Wright, 1949.
61. Penrose, L. S. The Distal Triradius t on the Hands of Parents and Sibs of Mongol Imbeciles. Ann. Hum. Genet. 19:10-38, 1954.
62. Turpin, R., and Caratzali, A. Conclusions d'une étude génétigue de la langue plicaturée. Comp rend. Acad. Sc. Paris. 196,2040-2042, 1933.
63. Penrose, L. S.; Ellis, J. R.; and Delhanty, J. D. A. Chromosomal Translocations in Mongolism and in Normal Relatives. Lancet II:409-410 (Aug. 20), 1960.
64. Carter, C. O.; Hamerton, J. L.; Polani, P. E.; Gunalp, A.; and Weller, S. D. V. Chromosome Translocation as a Cause of Familial Mongolism. Ibid. II:678-680 (Sept. 24), 1960.
65. Buckton, K. E.; Harnden, D. G.; Baikie, A. G.; and Woods, G. E. Mongolism and Leukaemia in the Same Sibship. Ibid. 1:171-172 (Jan. 21), 1961.
66. Hamerton, J. L.; Briggs, S. M.; Giannelli, F.; and Carter, C. O. Chromosome Studies in Detection of Parents with High Risk of Second Child with Down's Syndrome. Ibid. II:788-791 (Oct. 7), 1961.
67. Shaw, M. W., and Chu, E. H. Y. Chromosome Analysis of a Mother of Two Mongols. Presentation at Annual Meeting, American Society of Human Genetics, May 3, 1961 (abstract).
68. Ek, J. I.; Falk, V.; Bergman, S.; Reitalu, J. A Male Mongoloid with 46 Chromosomes. Lancet II:526-527 (Sept. 2), 1961.
69. Forssman, H., and Lehmann, O. Translocation—Carrying Phenotypically Normal Males and the Down Syndrome. Ibid. I:1286 (June 10), 1961.
70. Edwards, J. H., and Clarke, G. 1960. (After Penrose Ref. 8.)
71. Delhanty, J. D. A., and Penrose, L. S. 1961. (After Penrose Ref. 8.)
72. Miller, O. J. 1960. (After Penrose Ref. 8.)
73. German, J. L., III; De Mayo, A. P.; and Bearn, A. G. Chromosomal Translocation in a Mongol with Leukemia. Presentation at Annual Meeting, American Society of Human Genetics, 1961.
74. Fraccaro, M.; Kaijser, K.; and Lindsten, J. Chromosomal Abnormalities in Father and Mongol Child. Lancet I:724-727 (Apr. 2), 1960.
75. Lubs, H. A., Jr. Causes of Familial Mongolism. Ibid. II:881 (Oct. 14), 1961.
76. Carter, C. O., and Evans, K. A. Risk of Parents Who Have Had One Child with Down's Syndrome (Mongolism) Having Another Child Similarly Affected. Ibid. II:785-787 (Oct. 7), 1961.
77. Jervis, G. Mongolism in Twins. Am. J. Ment. Deficiency 47:364-369 (Apr.), 1943.

78. Allen, G., and Baroff, G. S. Mongoloid Twins and Their Siblings. Acta Genet. 5:294–326, 1955.
79. Ingalls, Theodore H. Pathogenesis of Mongolism. Am. J. Dis. Child. 73:279–292, 1947.
80. Johnston, A. W. The Chromosomes in a Child with Mongolism and Acute Leukemia. New England J. Med. 264:591–594 (Mar. 23), 1961.
81. Amaral, E. L., and Pearson, H. A. The Mongoloid Leukemic Syndrome. Med. Ann. Dist. Columbia 30,3:152–157 (Mar.), 1961.
82. Stewart, A.; Webb, J.; and Hewitt, D. Survey of Childhood Malignancies. Brit. M. J. 1:1495–1508, 1958.
83. Merritt, D. H., and Harris, J. S. Mongolism in Acute Leukemia. A Report of Four Cases. A.M.A. Am. J. Dis. Child. 92:41–44, 1956.
84. Krivit, W., and Good, R. A. Simultaneous Occurrence of Mongolism and Leukemia. Report of a Nationwide Survey. Ibid. 94:289–293 (Sept.), 1957.
85. a. Wald, N.; Borges, W. H.; Li, C. C.; Turner, J. H.; Harnois, M. C.; Kim, J.; and Rothberg, L. Epidemiologic and Cytogenetic Aspects of the Relationship Between Mongolism and Leukemia. Presentation at Annual Meeting, American Society of Human Genetics, May 3, 1961.
b. ————. Leukemia Associated with Mongolism. Lancet I:1228 (June 3), 1961.
86. Holland, W. W.; Doll, R.; Carter, C. O. The Mortality from Leukemia and Other Cancers Among Patients with Down's Syndrome (Mongols) and Among Their Parents. (In press.)
87. Mittwoch, U. The Relationship Between the Leucocyte Count, the "Shift to the Left" and the Incidence of Drumsticks in Mongolism. Proc. VII Internat. Congress Intern. Soc. Hematology III:475–480, 1958.
88. Uchida, I., and Curtis, E. J. A Possible Association Between Maternal Radiation and Mongolism. Lancet II:848–850 (Oct. 14), 1961.
89. Jacobs, P. Blood Cell Cultures for Cytodiagnostic Uses. Presentation at Blood-Bone Marrow Tissue Culture and Cell Separation Conference, Bethesda, Md., October 20, 1961.
90. Baikie, A. G.; Court-Brown, W. M.; Buckton, K. E.; Harnden, D. G.; Jacobs, P. A.; and Tough, I. M. A Possible Specific Chromosomal Abnormality in Human Chronic Myeloid Leukemia. Nature 188,4757: 1165–1166 (Dec. 31), 1960.
91. Tough, I. M.; Court-Brown, W. M.; Baikie, A. G.; Buckton, K. E.; Harnden, D. G.; Jacobs, P. A.; King, M. J.; and McBride, J. A. Cytogenetic Studies in Chronic Myeloid Leukemia and Acute Leukemia Associated with Mongolism. Lancet I:411–417 (Feb. 25), 1961.
92. Baikie, A. G.; Jacobs, P. A.; McBride, J. A.; and Tough, I. M. Cytogenetic Studies in Acute Leukemia. Brit. M. J. I:1564–1571 (June 3), 1961.
93. a. Schoyer, N. H. D. The Philadelphia Chromosome. Lancet I,7176:559 (Mar. 11), 1961.
b. Ibid. I,7181:826 (Apr. 15), 1961.
94. Blattner, R. J. Chromosomes in Chronic Myeloid Leukemia and in Acute Leukemia Associated with Mongolism. J. Pediat. 59,1:145–148 (July), 1961.
95. Warkany, J. Etiology of Mongolism. Ibid. 56,3:412–419 (Mar.), 1960.

Dr. Cohen and Dr. Lilienfeld are associated with the Department of Chronic Diseases, Johns Hopkins University School of Hygiene and Public Health, Baltimore, Md. Dr. Sigler is assigned to the Johns Hopkins School of Hygiene and Public Health by the Division of Radiological Health, Public Health Service.

This paper was presented before the Epidemiology Section of the American Public Health Association at the Eighty-Ninth Annual Meeting in Detroit, Mich., November 16, 1961.

This study was supported by Research Career Development Award No. GM-K3-5590-C1 and Grant CT-5085 from the National Cancer Institute, Public Health Service.

Reprinted from THE JOURNAL OF PEDIATRICS, St. Louis
Vol. 67, No. 4, Pages 631-642, October, 1965. (Printed in the U. S. A.)

Appendix B
Pub. #2

Parental age in Down's syndrome (mongolism)

Because of the new insight afforded by recent cytogenetic discoveries, the need for further clarification of the parental age effect in Down's syndrome was apparent. As part of an epidemiologic study of Down's syndrome in Baltimore, Maryland, the relative significance of maternal and paternal ages as etiological factors was evaluated. By comparing a control group matched by birth certificates, parental age was studied directly, first by controlling maternal, and then paternal ages. There was no statistically significant association between paternal age and Down's syndrome, but the relationship between Down's syndrome and increased maternal age remains unequivocal. Other observations are made about parental age in Down's syndrome and other trisomic conditions.

Arnold T. Sigler, M.D.,* Abraham M. Lilienfeld, M.D., M.P.H., F.A.P.M.H.,**
Bernice H. Cohen, M.P.H., Ph.D.,* and Jeanette E. Westlake, R.N., M.P.H.**

BALTIMORE, MD.

THE SEARCH for etiologic factors in Down's syndrome (mongolism) continues to focus on the significance of maternal and paternal ages. Of great recent significance was the discovery that the vast majority of cases of Down's syndrome show 47 chromosomes and are trisomic for chromosome No. 21. The parents of these children usually have no gross observable chromosomal abnormalities. The mechanism of this trisomy is thought to be nondisjunction, either in gametogenesis prior to fertilization, or at an early cleavage division of the zygote.

A smaller number of patients with Down's syndrome have 46 chromosomes with an abnormality involving an extra dose of the number 21 chromosome. These appear as translocations or duplications arising from chromosomal breaks. The parents of these children and other family members may have normal karyotypes, may be phenotypically normal carriers of the aberration, or may themselves be affected.

These cytogenetic findings require that, if an environmental stimulus is responsible for Down's syndrome, it must act prior to or very shortly after the time of conception. Thus, much of the vast accumulated genetic, anatomic, biochemical, and epidemiologic

From the Department of Chronic Diseases, Johns Hopkins School of Public Health, and Department of Pediatrics, Harriet Lane Home, Childrens Medical and Surgical Center, Johns Hopkins School of Medicine. Part of this study was performed while Dr. Sigler was assigned to the Research Branch, Division of Radiological Health, United States Public Health Service.

Supported by United States Public Health Service, Research Branch, Division of Radiological Health, Contract No. SAph 76367, and in part by National Cancer Institute No. CT 5085, and National Heart Institute No. HE 5297.

Some of the computations in this paper were done in the computing center of The Johns Hopkins Medical Institutions, which is supported by Research Grant, FR-00004 from the National Institutes of Health.

*Address, Department of Pediatrics, Johns Hopkins Hospital, Baltimore, Md. 21205.

**Recipient of a Research Career Award No. 5-K6-GM-13,901, The National Institute of General Medical Sciences.

***Recipient of a Research Career Development Award No. 5-K3-GM-5590, from The National Institute of General Medical Sciences.

evidence about this condition should be reevaluated and new investigations undertaken. Further clarification of the relationship between parental age and mongolism is essential to this new orientation.

It is now well established that the incidence of Down's syndrome increases sharply with advancing maternal age.[1-4] In addition, other evidence indicates that some cases of Down's syndrome are independent of maternal age.[1] Paternal age, in contrast, has always been considered etiologically insignificant, yet has never actually been studied by direct means. More recently, a small group of translocation cases of type 21-22 have been described in which paternal and not maternal age seems to be significant.[5] In addition, there are an increasing number of reports of other chromosomal aberrations in which advanced parental age appears to be important.[6-7] Because of the new insight afforded by these cytogenetic discoveries, the need for further clarification of the parental age effect is apparent.

The present study was designed with the following objectives in mind: firstly, to examine, by interview technique and medical record analysis, a population of parents of children with Down's syndrome and control mothers and fathers for exposure to certain envirnomental agents or health hazards postulated to cause nondisjunction; secondly, to study objectively and intensively the possible role of the father in the pathogenesis of the defect and finally, as a part of this comprehensive study, to examine the role of parental age in a direct fashion by using age-matching procedures.

Only the data dealing with aspects of parental age are presented in this publication.

MATERIALS AND METHODS

Selection of cases. The names of children with a diagnosis of mongolism were made available by the Maryland State Training School, special Baltimore private, county, parochial, and public schools, Baltimore hospitals, and private physicians. For the parents of a child to be eligible for interview, the child must have been (1) of Caucasian race, and (2) born in greater Baltimore after Jan. 1, 1946, and prior to Oct. 1, 1962. These criteria were imposed to limit the recall period to more recent events and to facilitate the location of hospital records. Although no attempt was made to ascertain every mongoloid infant born during this period, 421 cases were collected. After eliminating those who did not meet the study requirements, 288 children with a diagnosis of Down's syndrome were initially available to study. Of the cases excluded, 17 could not be located in the city directories, 51 were definitely not born in Baltimore and birth certificates could not be located for 8. Thirty-eight cases were not Caucasian and 17 were too old for the study.

Selection of control subjects. The birth certificates of the children with Down's syndrome were first located and their place of birth and other vital information verified. Control subjects were then selected by rigidly matching, in a systematic manner, each case with another birth certificate for (1) hospital of birth (or at home), (2) sex, (3) date of birth, and (4) maternal age at time of birth of the child. In each case the "best" control was a child of the same sex, born in the same hospital or at home (to a mother of the same age) and whose birth date was closest to that of the child with Down's syndrome. In some cases, the "best" control on the basis of the established criteria either had left the state or could not be located. In these instances, the next "best" control was selected—usually one with a slightly greater difference in birth dates—the other citeria remaining the same. Of the controls, 79.3 per cent were primary selections; 14.6 per cent were replaced with new controls once only, and 6.1 per cent were replaced more than once. All 288 cases (100 per cent) were matched with controls of identical sex, race, and hospital of birth (or home). The general results of the matching of maternal age and date of birth are shown in Table I. To evaluate further the role of parental age, the identical process was again carried out, but

Table I. Summary of matching between cases of Down's syndrome and controls

Maternal age groups	*No. of cases of Down's syndrome*	*Controls matched by:* Same birth date* and maternal age†		*Same birth date, different maternal age*		*Same maternal age different birth date*		*Different maternal age and birth date*	
		No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
< 19	9	9	100.0	—	2.1	—	—	—	—
20-24	47	43	91.5	1	5.0	3	6.4	—	—
25-29	40	36	90.0	2	3.3	2	5 0	—	—
30-34	60	55	91.7	2	2.4	3	5.0	—	—
35-39	82	78	95.2	2	4.3	2	2.4	—	—
40-44	46	23	50.0	19	41.3	2	4.3	2	4.4
> 45	4	—	—	3	75.0	—	—	1	25.0
Unknown	—	—	—	—	—	—	—	—	—
Total	288	244	84.7	29	10.1	12	4.2	3	1.0

*Same case birth date, within 6 months.
†Same maternal age, within 1 year.

Table II. Physical findings* in cases of Down's syndrome

Physical signs	*Physical signs present* No.	%
Brachycephaly	169	87.1
Slanted palpebral fissures	177	91.2
Epicanthic folds	155	79.9
Palmar simian lines	126	64.9
Malformed ears	160	82.5
Broad and/or short neck	147	75.8
Malformed fingers and/or hands	156	80.4
Nasal abnormality	177	91.2
Hypertelorism	186	95.9
Abnormal palate	164	84.5
Brushfield spots	107	55.2
Broad and/or short trunk	159	82.0

*Found on personal investigation (194 cases).

in reverse. This time paternal age at the time of birth of the child was matched, in addition to race, sex, date of birth, and hospital of birth. All of these cases were matched with controls of identical sex, race, and hospital of birth. There were only minor differences between matched paternal ages and dates of birth of the index cases. The new control maternal ages were taken from each of the matched birth certificates and were compared to the original cases of Down's syndrome. Maternal age was the only variable studied with paternal age controlled. Because of reasons to be discussed below, a certain number of cases were eliminated from the study, and thus, less than the original 288 cases were ultimately used in the final analysis.

Verification of diagnosis. A set of physical criteria for Down's syndrome, based on the consistently observed findings as previously reported,[4-8] was established. These criteria were selected also because they were observable on inspection of the child rather than by formal examination. These "primary" criteria, together with their frequency in this population of cases of Down's syndrome are shown in Table II.

Each available case of Down's syndrome was examined by the senior author (A. T. S). The diagnosis and inclusion of a child into the study was confirmed if (A) on personal inspection the child was mentally retarded and had at least 6 of the listed primary signs; or (B) the diagnostic criteria (at least 7 in number) were actually listed by a qualified observer on a medical record. The statement on a chart that "this child is a mongol" did not satisfy the criteria. When medical records only were available to confirm the diagnosis (such as in those cases where the index child was deceased) other combinations of charted confirmatory data were used. Diagnosis was also accepted where five primary signs were listed plus evidence of either congenital heart disease, abnormal hip angles, or chromosomal studies. Of 254 cases submitted for diagnosis, 236 or 92.8 per cent were verified as correct: 155 on personal examination, 55 on both personal examination

and hospital rcords, and 26 on hospital records only. The total number of verifications is in excess of the 216 cases ultimately accepted since some cases were later eliminated for other reasons. Nine patients, most of whom were deceased, had to be eliminated because their available medical records did not list the required number of signs to confirm the diagnosis. Another 3.5 per cent were rejected on personal examination because of negative or equivocal diagnosis.

The hospital records as well as birth certificates of all control children were examined to be certain that the "normal" control group contained no cases of Down's syndrome.

Composition of final study group. Although 288 cases were originally available for study, 72 of these were eliminated for the reasons listed below, leaving 216 families with Down's syndrome and matched control families for the final analysis.

Conditionally accepted for study	288
Eliminated because of:	
Incorrect or equivocal diagnosis	18
Refusal of parents of patients with Down's syndrome to cooperate	17
Inability to locate family with Down's syndrome	15
Inability of family with syndrome to give adequate interview	2
Refusal of control to cooperate	20
Accepted for final analysis	216

RESULTS

Paternal age. The paternal age distribution for the cases of Down's syndrome and controls, matched by maternal age, are shown in Table III and Fig. 1; in addition, Fig. 1 contains the paternal age distributions of white births in Baltimore during 1946-1962. There is a marked increase in the ages of the Down's fathers as compared with the fathers of all white children born during the same time period in Baltimore. The mean age for the fathers in the syndrome group was 34.9 years as compared to 30.3 in the Baltimore population. In contrast to this difference in paternal age was the result obtained by a comparison of cases and con-

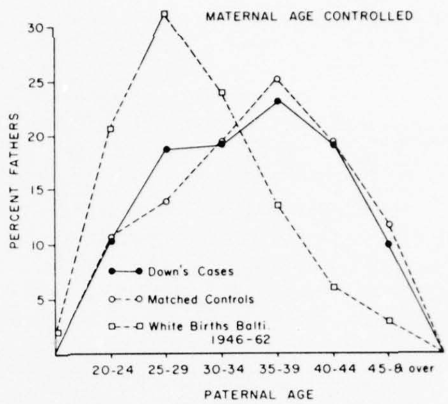


Fig. 1. Paternal age distributions in cases of Down's syndrome, matched controls, and in white births (Baltimore, 1946-1962) with maternal age controlled.

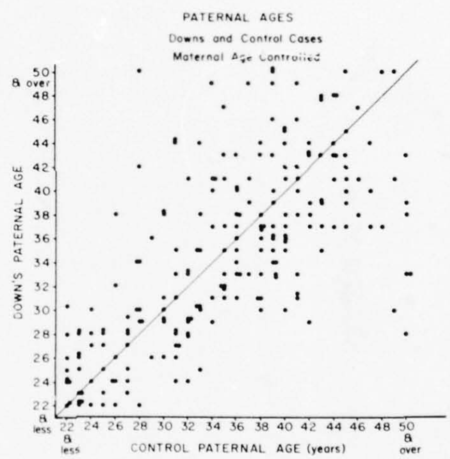


Fig. 2. Scattergram of matched Down's syndrome and control cases as to paternal ages with maternal age controlled.

trols matched by maternal ages and the other variables as previously discussed. The mean age of 34.9 years for the fathers in the syndrome group was almost identical to the mean age of 35.1 for the controls.

In addition, the age distributions of the fathers in both groups are quite similar.

A more precise comparison of the paternal age difference is observable when the corresponding paternal ages of each of the 215 matched pairs is plotted on a scattergram.

Table III. Distribution of pairs of cases and controls by maternal and paternal age, matched by maternal age*

	Mother				*Father*			
	Down's		*Controls*		*Down's*		*Controls*	
Age	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
15-19	6	2.8	6	2.8	—	—	—	—
20-24	34	15.7	32	14.8	22	10.2	23	10.6
25-29	30	13.9	33	15.3	40	18.5	30	14.0
30-34	47	21.8	48	22.2	41	18.9	42	19.4
35-39	62	28.7	62	28.7	50	23.4	54	25.0
40-44	35	16.2	35	16.2	41	18.9	42	19.4
45>	2	0.9	—	—	21	9.7	25	11.6
Unknown	—	—	—	—	1	0.4	—	—
Total	216	100	216	100	216	100	216	100

*The slight difference in the number of control and mothers with Down's syndrome in each age group is due to the arrangement of the cases into 5 year age groups.

Table IV. Matched pair analysis of paternal age with maternal age controlled (paired t test)

	Down's paternal age—control paternal age						
Maternal age group	*No. of fathers*	$\Sigma\ d$	$\Sigma\ d^2$	*Mean difference*	*S.D.*	*t*	*p Value*
15-19	6	0	38	0	2.8	0	N.S.
20-24	34	0	616	0	4.3	0	N.S.
25-29	30	−2	1,012	−.07	5.9	.07	N.S.
30-34	46	−141	1,813	−3.07	5.5	3.79	<0.001
35-39	62	+28	3,576	+.45	7.6	0.66	N.S.
40>	37	+42	1,532	+1.1	6.4	1.05	N.S.
All cases*	215	−73	8,587	−0.34	6.3	0.79	N.S.

*Because the paternal age was unavailable on one father, the analysis was carried out on 215 matched pairs.

Fig. 2 shows that when paternal ages in the group with Down's syndrome are plotted against the controls, there is no preponderance of points either above or below the diagonal. The majority of age-pairs are clustered along the diagonal indicating a similarity of ages for the two groups. There are a number of outstanding exceptions where, in a number of cases, the age of the father in the group with Down's syndrome greatly exceeds that of the control, but the reverse is also true.

A matched pair analysis by the use of paired t test technique carried out on each age-pair confirmed these findings (Table IV). When the total 215 cases were analyzed, there was no significant difference between the fathers in the Down's group and controls ($t = 0.79$). Moreover, when analyzed by 5 year maternal age groups, there were no significant differences except in the 30-34 maternal age group. However, the data do suggest the possibility of an interesting pattern: in the younger maternal ages (under 35), the Down's syndrome group fathers are younger than the controls, whereas among the older mothers (35 and over), the case fathers are older than the controls. Since this is an ex post facto observation, one should not attribute any significance to it; however, it is of sufficient interest to warrant further validation in an independent set of data.

Maternal age. The maternal age distributions for the total 215 matched cases is shown in Fig. 3. Since the cases of Down's syndrome and controls were first matched for maternal age, the distributions are practically identical. However, they do demonstrate the characteristic increase in maternal age in Down's syndrome when compared to all white mothers in Baltimore between 1946

and 1962. The mean age for mothers of children with Down's syndrome is 32.5 as compared to 26.6 for the general Baltimore population. The distribution curve for these mothers is bimodal, with the main peak at the 35-39 age group and the lesser peak at the 20-24 age group. In addition, the lesser peak at age 20-24, corresponds exactly with the maximum peak for all births from the general population.

Since maternal and paternal ages are closely correlated, and because the effects of each have been difficult to separate in Down's syndrome, it was felt essential to reverse the matching procedure and examine the maternal ages with the fathers' ages held constant. This was again accomplished by the use of birth certificates: new control fathers were matched with the fathers of children with Down's syndrome for paternal age, date of birth of the child, hospital of birth, sex, and race of the child. The new control maternal ages (as listed on the birth certificates) were *then compared with the* mothers.

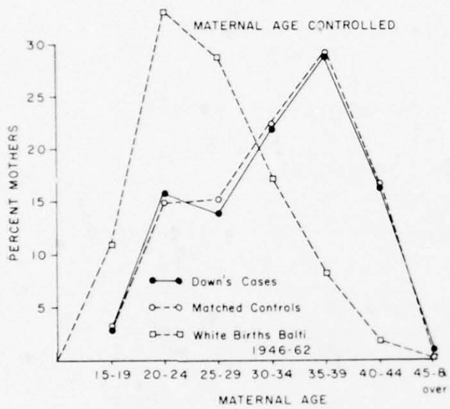


Fig. 3. Maternal age distributions in cases of Down's syndrome, matched controls, and white births (Baltimore, 1946-1962) with maternal age controlled.

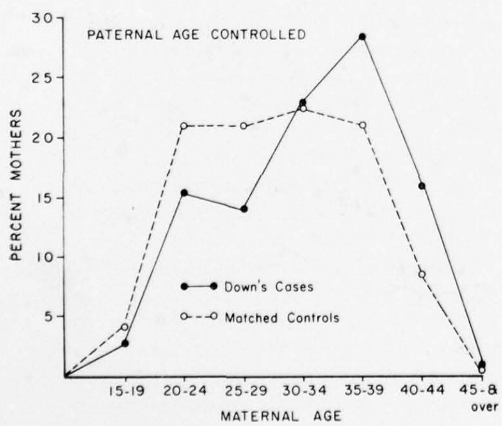


Fig. 4. Maternal age distributions in cases of Down's syndrome and in matched controls with paternal age controlled.

The maternal age distributions of these mothers and the matched controls, with paternal age controlled, are shown in Table V and Fig. 4. It is clear that, in the syndrome group, there is an excess of mothers in the older maternal age groups and that these mothers are a distinctly older population than the matched controls. The mean age of the mothers is 32.5 in the syndrome group as compared to 30.2 for the controls. The difference in maternal ages, however, is not nearly as great as that demonstrated when these mothers are compared to the general Baltimore population—mean age 25.6.

The maternal age of each of the cases is plotted, with its matched control, on a scattergram in Fig. 5. There is a concentration of the plotted points away from the diagonal toward the maternal age axis, further demonstrating the increased maternal age in the Down's syndrome group.

The marked statistical significance of the maternal age effect, as opposed to paternal age effect, is illustrated in Table VI. The relationship of each case to its matched control is again analyzed by use of the paired t test. The total mean age difference was 2.3 years older for the syndrome group mothers than controls. This corresponds to a t value of 6.05 which is very highly significant ($p < 0.001$).

DISCUSSION

Since 1933, when Penrose[9] and Jenkins[2] eliminated any paternal age effect in Down's syndrome, there has been practically no

Table V. Distribution of pairs of cases and controls by maternal and paternal age, matched by paternal age

	Father				*Mother*			
	Down's		*Controls*		*Down's*		*Controls*	
Age	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
15-19	—	—	—	—	6	2.8	9	4.1
20-24	22	10.2	22	10.2	33	15.3	47	21.9
25-29	40	18.6	40	18.6	30	14.0	47	21.9
30-34	41	19.1	41	19.1	49	22.8	48	22.3
35-39	51	23.7	53	24.7	61	28.4	45	20.9
40-44	41	19.1	41	19.0	34	15.8	18	8.4
45>	20	9.3	18	8.4	2	0.9	1	0.5
Total*	215	100	215	100	215	100	215	100

*Because the paternal age in one case of Down's syndrome was unavailable, the distributions and analyses contain 215 cases.

Table VI. Matched pair analysis of maternal age with paternal age controlled (paired t test)

	Down's maternal age—control maternal age						
Paternal age group	*No. of mothers*	$\Sigma\ d$	$\Sigma\ d^2$	*Mean difference*	*S.D.*	*t*	*p Value*
20-24	22	−2	182	−0.09	3.0	0.14	N.S.
25-29	40	+29	817	+0.73	4.5	1.03	N.S.
30-34	41	+140	2,278	+3.4	6.7	3.09	<0.01
35-39	53	+122	1,988	+2.3	5.7	6.28	<0.001
40-44	39	+191	1,831	+4.9	4.9	6.20	<0.001
45>	20	+16	914	+0.80	6.9	0.53	N.S.
All cases	215	+496	8,010	2.3	5.7	6.05	<0.001

further study of the etiological role of the father. In retrospect, this omission is probably not justifiable since Penrose's analysis was an indirect one, and there has never been any direct evidence against the father having at least some part in the causation of the condition. That this was precisely the case has recently been shown by the discovery of familial chromosomal abnormalities in a small number of these fathers.[10-12] Penrose, in fact, has recently modified his original thesis to include a few fathers with *21-22* fusions who seem to have elevated ages as compared to the mothers.[5]

Because of the close correlation between maternal and paternal age in general, it has always been difficult to evaluate the degree of association that either might have with Down's syndrome. In this study, maternal age was carefully controlled (in addition to other variables) and paternal age was studied in a direct fashion. Although the fathers in the Down's syndrome group are an average 4.5 years older than the paternal ages of all white births in Baltimore during 1946-1962, when compared to the matched controls, there is no over-all significant difference between the two groups. However, when arranged by maternal age, the fathers of children with Down's syndrome are 0.71 years older than the controls for those mothers 35 and over. Prior to maternal age 35, in contrast, the control fathers are 1.23 years older than the Down's. This finding may be consistent with Penrose's observation that some types of Down's syndrome are correlated with increased paternal age. However, in contrast to the major relationship of Down's syndrome and maternal age, any paternal age effect remains a small one.

The association of older mothers with Down's syndrome is now indisputable. The procedure utilized in the present study demonstrates, unequivocally, the positive relationship with maternal age. However, one aspect of the maternal age distribution is

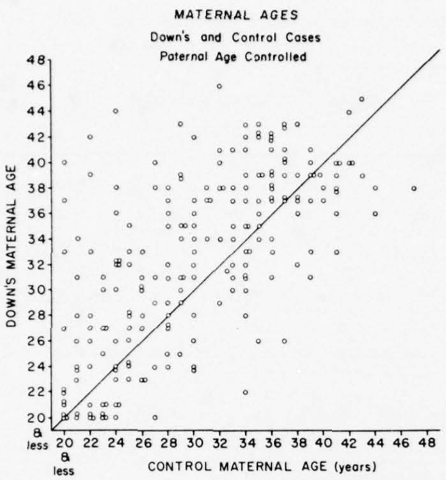


Fig. 5. Scattergram of matched Down's syndrome group and control group maternal ages with paternal age controlled.

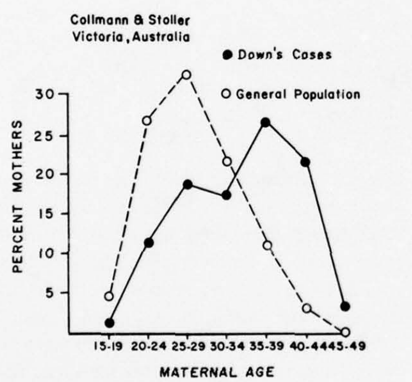


Fig. 6. Maternal age distributions for all births and births of infants with Down's syndrome in Victoria, Australia (1942-1957).

worthy of further comment, namely the finding of a smaller peak in the maternal age distribution at the younger ages resulting in bimodality. This bimodality has been alluded to by Penrose,[20, 21] Øster,[22] Collmann and Stoller,[23] and others. More recently, it has been attributed to the presence of translocation and other familial chromosomal abnormalities.[24] However, it is probable that this peak does not represent an excess of cases of Down's syndrome at all, since the corresponding actual age specific incidence rates (Table VII) fail to show a peak in the younger age groups. Instead, there is virtually no change in the incidence of Down's syndrome until the age of 30 is exceeded. However, it is possible that the early peak shown in the age distribution is a statistical artifact and reflects the large number of births to mothers between the ages of 20 and 29 in the general population. Even though the incidence of classical age-dependent trisomy is very low in the younger age groups, a relatively large number of cases of Down's syndrome can be expected because of the high birth rate below the age of 30. Similarly, translocation and familial Down's syndrome is probably age independent, and the largest number of cases can be expected in the younger maternal age groups where birth rates are the highest.

This explanation is strengthened by examination of the data of other investigators. The maternal age distributions of over 1,000 cases of Down's syndrome gathered by Collmann and Stoller[23] is shown in Fig. 6. This distribution also shows a sharp secondary peak, in the 25-29 age group, which is also the group containing the most births in the Victoria population. Thus, in both our own population and in Victoria, Australia, the early peak in the material distribution of cases of Down's syndrome corresponds exactly to the maternal age peak in the general population. The maternal age distribution in cases of Down's syndrome of other independent populations reported by Øster[4] and Carter and MacCarthy[3] also demonstrate this effect, although less prominently. It should be emphasized, though, that the corresponding age specific incidence figures for each of these populations are very similar.

That the secondary peak (in the younger ages) in the maternal age distribution is a result of the maternal age distribution of the total births, may be demonstrated as follows: two theoretical, populations of births have been developed and the maternal age distributions of each are shown in Table VII. (The shape of these curves is similar to actu-

Table VII. Theoretical maternal age distributions of two populations,* demonstrating the movement of the early Down's maternal age peak with actual age specific incidence rates held constant.

Maternal age	Age specific incidence per 1,000 births† (actual)	No. of births in general populations (theoretical)		No. and per cent of cases of Down's syndrome expected			
				Pop. A		Pop. B	
		Pop. A	Pop. B	No.	%	No.	%
15-19	0.00	10,000	10,000	0	00.0	0	00.0
20-24	0.28	71,428	103,448	20	12.5	29	18.1
25-29	0.29	103,448	71,428	30	18.8	21	13.1
30-34	1.72	15,116	15,116	26	16.2	26	16.2
35-39	3.52	12,500	12,500	44	27.5	44	27.5
40-44	14.18	2,397	2,397	34	21.2	34	21.3
45 and over	26.32	227	227	6	3.8	6	3.8
Total	1.51	215,116	215,116	160	100	160	100

*These theoretical populations are similar in shape to actual populations and are similar to one another except for a reversal between the 20-24 and 25-29 age groups in regard to number of births.

†Age specific incidence rates from Carter and MacCarthy.[3]

al populations.) In Population A, the peak in the maternal age distribution for total births has been placed in the 25-29 age group, and in Population B, the peak has been placed in the 20-24 age group. By applying the same age specific incidence rates[3] for Down's syndrome to each of these theoretical populations, the number of cases of Down's syndrome expected for each maternal age group can be calculated. The result is that in each population, peaks are produced in the maternal age distribution for cases of Down's syndrome which correspond exactly to the peaks in the theoretical populations. The effect has been the movement of the Down's secondary maternal age peak from age group 25-29 up to group 20-24 (Table VII and Fig. 7).

It is important to emphasize that a biological inference of maternal age effects should be derived only from age-specific incidence rates which measure the risk of Down's syndrome by maternal age rather than from maternal age distributions which reflect both incidence rates and maternal age distributions of total births.

It is apparent, both from the comparisons made within the data presented here and with the data of others, that the selection of controls is vital to the study of parental age. First, the mean age or age distribution of one population cannot be used as a comparison with another, nor can the total incidence rates for a condition such as Down's syndrome be applied to a population other than that from which they were derived. This becomes obvious from examining the differences between maternal ages in Baltimore, Victoria, Australia, Denmark, or England as presented in Table VIII. The mothers of white infants born in Baltimore during 1946-1962 are younger than the mothers in the other populations. This is reflected both in the lower mean maternal age and also the large number of mothers under age 30 in Baltimore. Although accurate incidence figures are not available, it can be postulated that the *total* incidence of Down's syndrome may be less in Baltimore than in other populations.

It is also possible that, in some instances, even the general population from which the cases are drawn may not serve as a good control group for the study of parental age. This is true because socioeconomic and cultural factors are strong determinants of when parents produce children.[25] In addition, the use of mean ages, drawn from general populations, will often demonstrate marked differences in age, but may not distinguish smaller effects, or interparental effects. In this study, in Down's syndrome, the mean

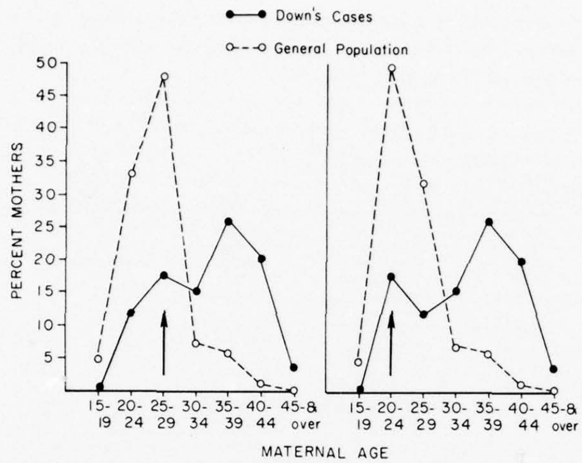


Fig. 7. Theoretical distributions of general populations A (left) and B (right) with corresponding distributions of cases of Down's syndrome using the same age specific incidence rates on each population. The effect is the movement of the secondary maternal age peak in Down's syndrome from age group 25-29 to group 20-24.

Table VIII. Summary of mean maternal ages of births in various populations with corresponding partial per cent distributions of younger mothers

	Mean ages of mothers (years)		*Per cent of general population with maternal age*			
	Down's	*Control population*	*15-19*	*20-24*	*25-29*	*Total < 30*
Baltimore study (1946-1962)	32.5	26.6	12.0	32.5	27.7	72.2
Victoria Collman and Stoller (1942-1957)	33.7	27.9	4.5	26.6	32.5	63.6
Denmark Øster (1959)	35.1	28.7	4.4	26.9	30.9	62.2
England Carter and MacCarthy (1949)*	36.9	28.6	5.6	25.3	30.4	61.3

*Calculated from data in this publication.

age for the mothers is 32.5 and for fathers, 34.9. The mean ages calculated from the general Baltimore white population for years 1946-1962 are 26.6 and 30.3 for mothers and fathers, respectively. There is obviously a very highly significant increase in both the maternal and paternal mean ages in Down's syndrome as compared to the Baltimore parents.

Because of this increased age, and because of the smaller mean age difference (1.3 years) between the Down's parents and total Baltimore white parents, a primary maternal age effect might be assumed. Actually, there is no good method of assessing the contribution of either maternal or paternal age when mean ages are compared. The only reasonable conclusion is that both the mothers and fathers of children with Down's syndrome are different from the general population. The present study, in contrast, by controlling first maternal and then paternal

age, makes possible a direct evaluation of the relative contribution of each parent.

The implications of these findings extend to other conditions as well. The newly described D and E trisomy syndromes have stimulated further interest in the etiology of nondisjunction. These conditions have also been associated with increased maternal age,[6, 7, 26] and would thus involve some of the objections already discussed. Smith,[6] for instance, compares the average maternal age of D_1 and 18 trisomies (1962—from various sources) to the mean age of Down's and control groups from births in England and Wales in 1939 as reported by Penrose.

Hecht and co-workers[7] concluded that nondisjunction in trisomy 17-18, as in Down's syndrome, is mainly maternal, because the mean paternal-maternal age difference for the cases was 1.7 as compared with 3.5 years in the control populations of all United States births in 1960. However, the mean ages of both the fathers (36.0) and mothers (34.3) of trisomics are much greater than the controls (29.9 and 26.4), and thus these conclusions must be tempered with caution. The cases in this series, for instance, are collected from numerous sources and also from different countries, yet the parental ages are grouped and compared to the mean parental ages for all of the births in the United States during 1960. However, in view of the demonstrated varibility in parental ages (Table VII), the control data used by Hecht and co-workers are unsatisfactory. Clearly, the demonstration of a smaller maternal-paternal age difference in these trisomy 17-18 cases does not justify the conclusion that maternal nondisjunction is "the single most important cause of the syndrome."[7]

It should be emphasized that failure to show a significant relationship with paternal age does not warrant the elimination of the father from etiologic consideration. Since Down's and other trisomy syndromes occur at all parental ages, correlation with age must be considered as only a guide in the search for the actual causal factors. Additional data obtained in the field study described in this paper will provide further observations on possible paternal and maternal factors.

SUMMARY AND CONCLUSIONS

The relative significance of maternal and paternal ages were evaluated as part of an epidemiologic study of Down's syndrome in Baltimore, Maryland. By the use of a control group matched by birth certificates, parental age was studied directly, first by controlling maternal, and then paternal ages. There was no positive statistical association of paternal age with Down's syndrome. The relationship between Down's syndrome and increased maternal age, however, remains unequivocal.

The early secondary peak reported previously in maternal age distribution in Down's syndrome was again found, and shown to be an artifact—a reflection of the high frequency of total births at this maternal age. Selection of reliable control data in the study of the parental age effect, both in Down's and other syndromes, was stressed; the adequacy of control ages used in the study of the parental age effect in other trisomic conditions is questioned.

We wish to acknowledge the contributions of Dr. William Hetznecker who helped institute this study, Mrs. Susan Baker who was responsible for the computer programming, Miss Elaine Glassband for her technical assistance, and Dr. Robert Cooke, Dr. Barton Childs, and Dr. Simon Abrahams for their helpful suggestions. In addition, generous cooperation and support was given by Mr. Sidney Norton of the Department of Vital Statistics, by the Baltimore Society for Retarded Children, the principals of the many schools for the retarded, and the administrators and medical records personnel of the Baltimore hospitals.

REFERENCES

1. Penrose, L. S.: Mongolism, Brit. M. Bull. **17:** 184, 1961.
2. Jenkins, R. L.: Etiology of mongolism, Am. J. Dis. Child. **45:** 506, 1933.
3. Carter, C., and MacCarthy, D.: Incidence of mongolism and its diagnosis in the newborn, Brit. J. Social Med. **5:** 83, 1951.
4. Øster, J.: Mongolism. A clincogenealogical investigation comprising 526 mongols living in Finland and neighboring islands in Den-

mark, Copenhagen, 1953, Danish Sc. Press, Ltd.
5. Penrose, L. S.: Paternal age in mongolism, Lancet 1: 1101, 1962.
6. Smith, D. W.: The No. 18 trisomy and D_1 trisomy syndromes, Pediat. Clin. North America 10: 389, 1963.
7. Hecht, F., Bryant, F. S., Motulsky, A. G., and Gilbett, E. R.: The No. 17-18 (E) trisomy syndrome, J. PEDIAT. 63: 605, 1963.
8. Benda, C.: The child with mongolism, New York, 1960, Grune & Stratton, Inc.
9. Penrose, L. S.: The relative effects of paternal and maternal age in mongolism, J. Genetics 27: 219, 1933.
10. Forssman, H., and Lehmann, O.: Translocation carrying phenotypically normal males and the Down syndrome, Lancet 1: 1286, 1961.
11. Fraccaro, M., Kaijser, K., and Linsten, J.: Chromosomal abnormalities in father and mongol child, Lancet 1: 724, 1960.
12. Sergovich, F. R., Soltan, H. D., and Carr, D. H.: A 13-15/21 translocation chromosome in carrier father and mongol son, Canad. M. A. J. 87: 852, 1962.
13. Frost, J. N.: Autosomal non-disjunction in males of drosophila melanogaster, Genetics 46: 40, 1961.
14. Stern, C.: On the occurrence of translocations and autosomal non-disjunction in drosophila melanogaster, Proc. Nat. Acad. Sc. 20: 36, 1934.
15. Morgan, T. H., Bridges, C. B., and Sturtevont, A. H.: The genetics of drosophila, Bibliogr. Genetica 11: 3, 1925.
16. Russell, L. B., and Chu, E. H.: An XXY male in the mouse, Proc. Nat. Acad. Sc. U.S. 47: 571, 1961.
17. Bishop, P. M. F., Lessof, M. H., and Polani, P. E.: Turner's syndrome and allied conditions, Mem. Soc. Endocrinol. 7: 162, 1960.
18. Lennox, B.: Indirect assessment of number of X chromosomes in man, using nuclear sexing and colour vision, Brit. M. Bull. 17: 196, 1961.
19. McKusick, V. A.: On the X chromosome of man, Quart. Rev. Biol. 37: 69, 1962.
20. Penrose, L. S.: Mongolian idiocy (mongolism) and maternal age, Ann. New York Acad. Sc. 57: 494, 1953-1954.
21. Penrose, L. S.: Maternal age in familial mongolism, J. Ment. Sc. 97: 738, 1951.
22. Øster, J.: The causes of mongolism, Danish M. Bull. 3: 158, 1956.
23. Collmann, R. D., and Stoller, A.: A survey of mongoloid births in Victoria, Australia, 1942-1957, Am. J. Pub. Health 52: 813, 1962.
24. Polani, P. E.: Cytogenetics of Down's syndrome, Pediat. Clin. North America 10: 2, 1963.
25. MacMahon, B., Pagh, T. F., and Ipsen, J.: Epidemiologic methods, Boston, 1960, Little Brown & Company.
26. Uchida, I. A., Bowman, J. M., and Wang, H. C.: The 18-trisomy syndrome, New England J. Med. 266: 1198, 1962.

Appendix B
Pub. #3

Reprinted from BULLETIN OF THE JOHNS HOPKINS HOSPITAL
Vol. 117, No. 6, pp. 374-399, December, 1965
Printed in U.S.A.

RADIATION EXPOSURE IN PARENTS OF CHILDREN WITH MONGOLISM (DOWN'S SYNDROME)[1, 2]

ARNOLD T. SIGLER,[3] ABRAHAM M. LILIENFELD,[4] BERNICE H. COHEN,[4]
AND JEANNETTE E. WESTLAKE

Department of Chronic Diseases, The Johns Hopkins University School of Public Health, and Department of Pediatrics, Harriet Lane Home, Childrens Medical and Surgical Center, The Johns Hopkins University School of Medicine

Received for publication June 10, 1965

With the discovery that the majority of individuals with Mongolism are trisomic for chromosome 21, attention has been focused on the time period prior to conception and on gametogenesis in search of an explanation for the error of non-disjunction.

Because of the known relationship between ionizing radiation and chromosomal aberrations including non-disjunction in Drosophila, laboratory animals and man (1–11), the association of leukemia and Mongolism (12–14), and the widely accepted leukemogenic effect of radiation (15–21), a significant link between ionizing radiation and Mongolism was considered a reasonable possibility.

The recent cytogenetic and epidemiologic observations stimulated the present study of the possible relationships between Mongolism and ionizing radiation prior to or around the time of conception. As part of an epidemiologic investigation utilizing interview technique and medical record analysis, a group of mothers and fathers of children with Mongolism and control subjects were evaluated for exposure to various types of radiation.

[1] Supported by United States Public Health Service, Research Branch, Division of Radiological Health, Contract No. SAph 76367 and in part by National Cancer Institute No. CT 5085 and National Heart Institute No. HE 5297.

[2] Some of the computations in this paper were done in the computing center of the Johns Hopkins Medical Institutions, which is supported by Research Grant, FR-00004 from the National Institutes of Health.

[3] Part of this study performed while Dr. Sigler was assigned to the Research Branch, Division of Radiological Health, U.S.P.H.S.

Address: Department of Pediatrics, The Johns Hopkins Hospital, Baltimore, Maryland 21205.

[4] Dr. Lilienfeld is a recipient of a Research Career Award No. 5-K6-GM-13,901 and Dr. Cohen is a recipient of a Research Career Development Award No. 5-K3-GM-5590, both from The National Institute of General Medical Sciences.

MATERIALS AND METHODS

A. *Selection of Cases*

The names of children with a diagnosis of Mongolism were made available by the Maryland State Training School, special Baltimore private, county, parochial and public schools, Baltimore hospitals and private physicians. For the parents of a child to be eligible for interview, the child must have been 1) of Caucasian race, and 2) born in greater Baltimore after January 1, 1946 and prior to October 1, 1962. These criteria were imposed to limit the recall period to more recent events and to facilitate the location of hospital records. Although no attempt was made to ascertain every Mongol born during this period, 419 cases were collected. After eliminating those who did not meet the study requirements, 288 cases of Mongolism (not yet verified by physical examination) were initially available for study. Of the cases eliminated, 17 could not be located in the city directories; 51 were definitely not born in Baltimore; birth certificates could not be found for eight; 38 cases were not Caucasian; and 17 were too old for the study.

B. *Selection of Controls*

The birth certificates of the children with Mongolism were first located and their place of birth and other vital information verified. Controls were then selected by matching, in a systematic manner, each case with another birth certificate for 1) hospital of birth (or at home), 2) sex, 3) date of birth, and 4) maternal age at time of birth of the child.

All 288 cases (100 per cent) were matched with controls of identical sex, race, and hospital of birth (or home). The general results of the matching of maternal age and date of birth are shown in Table I. Because of reasons to be discussed below, a certain number of cases were eliminated from the study, and thus fewer than the original 288 cases were ultimately used in the final analysis.

C. *Contact and Interview of Parents*

After each family was located, a form letter describing the study as an "investigation" of parental and child health factors was mailed. The same letter was sent to both the Mongol and control families, and no mention was made of Mongolism in this communication. The mother and father were then interviewed, usually independently, in the home. The approach to both the families of the Mongols and controls was uniform; the interviewers were not informed which were cases and controls, and recognition

TABLE I

Summary of Matching between Mongols and Controls

Maternal Age Groups	No. of Mongols	Controls Matched By:							
		Same Birth Dates* & Maternal Age†		Same Birth Date, Dif. Maternal Age		Same Mat. Age Dif. Birth Date		Dif. Mat. Age & Birth Date	
		No.	%	No.	%	No.	%	No.	%
19 or less	9	9	100.0	—	—	—	—	—	—
20–24	47	43	91.5	1	5.0	3	6.4	—	—
25–29	40	36	90.0	2	3.3	2	5.0	—	—
30–34	60	55	91.7	2	2.4	3	5.0	—	—
35–39	82	78	95.2	2	4.3	2	2.4	—	—
40–44	46	23	50.0	19	41.3	2	4.3	2	4.4
45 or more	4	—	—	3	75.0	—	—	1	25.0
Total	288	244	84.7	29	10.1	12	4.2	3	1.0

* Same case birth date—within 6 months.
† Same maternal age—within 1 year.

of the Mongol's family was not usually made until the actual interview was conducted.

Out of the 288 cases and 288 controls initially selected for study, interviews were obtained on 87.5 per cent of the mothers and 85.8 per cent of the fathers of the Mongols and on 86.1 per cent and 85.4 per cent of the matched control mothers and fathers respectively. In every case where a family refused to cooperate, the corresponding matched case or control was also eliminated from analysis. There were only minor differences in success of interviewing both groups. Only 5.5 per cent of mothers of Mongols and 7.6 per cent of the control mothers refused to cooperate, while 5.9 per cent of the Mongol fathers and 7.6 per cent of the control fathers also refused.

D. *Method of Questioning*

Questions about radiation exposure were always phrased without reference to the birth of the index child. For instance, "Have you, anytime during your life, had x-rays or radiation for gallbladder disease? If so give the dates and places where this occurred." Only later, during the analysis, were these radiation occurrences enumerated and placed in the time period either prior to or following the birth of the Mongol or control.

E. *Medical Records*

A simultaneous study of several characteristics of the parents was carried out by examining hospital records. A list of every parental name in the study, both married and maiden, was submitted to every hospital in the city of Baltimore. This was performed independently and irrespective of

the information obtained on interview. If a record of attendance at the hospital was available, the chart was reviewed in entirety for 1) medical diagnosis during both in and out-patient visits, 2) surgical diagnoses and procedures and 3) x-ray or other radiation exposures.

F. *Verification of Diagnosis*

A set of physical criteria for Mongolism based on the most consistently observed findings, as previously reported (22, 23) was established. These "primary" criteria included brachycephaly, slanted palpebral fissues, epicanthic folds, palmar simian lines, malformed ears, broad &/or short neck, malformed fingers &/or hands, nasal abnormality, hypertelorism, abnormal palate, Brushfield spots, and broad &/or short trunk. Each available case of Mongolism was examined by the senior author (A.T.S.).

The diagnosis and inclusion of a child into the study was confirmed if (A) on personal inspection the child appeared mentally retarded and had at least six of the primary signs; or (B) the diagnostic criteria (at least seven in number) were actually listed by a qualified observer on a medical record. The statement on a chart that "this child is a Mongol" did not satisfy the criteria.

On the basis of the study criteria, the diagnosis of Mongolism was verified in 236 or 92.8 per cent of the cases. Of these, 155 diagnoses were based on physical examination alone, 55 on both personal examination plus hospital records and 26 from hospital records alone. Nine cases, or 3.6 per cent, most of whom were deceased, were eliminated because their available medical records did not list the required number of signs to confirm the diagnosis. Another 3.5 per cent were rejected on personal examination because of negative or equivocal diagnosis. The total number of cases is in excess of the 216 Mongols (all verified) ultimately accepted since some cases were later eliminated for other reasons.

G. *Composition of Final Study Group*

Although 288 cases were originally available for study, 72 of these were eliminated for the reasons listed below, leaving 216 Mongol families and matched control families for the final analysis.

Conditionally Accepted to Study:	288
Eliminated because of:	
Incorrect or equivocal diagnosis:	18
Mongol's parents refused to cooperate:	17
Unable to locate Mongol's family:	15
Mongol's family unable to give adequate interview:	2
Control refused to cooperate:	20
Accepted for Final Analysis:	216

AD-A061 593 JOHNS HOPKINS UNIV BALTIMORE MD SCHOOL OF HYGIENE A--ETC F/G 6/18
PARENTAL RADIATION AND DOWN'S SYNDROME, WITH PARTICULAR ATTENTI--ETC(U)
JUN 76 B H COHEN DADA17-69-C-0154
UNCLASSIFIED NL

4 OF 5
AD
A061 593


=5
593

RESULTS

I. *Residential History*

It was essential to study residential history to 1) evaluate possible differences in background radiation exposure, 2) rule out differences in medical exposure based on geographical proximity to medical facilities, and 3) insure that the risk of being irradiated in a Baltimore hospital was not affected by differences in the duration of residence in Baltimore.

Sixty-one and one-tenth per cent[5] of the mothers of Mongols and 57.9 per cent of the control mothers were born in Metropolitan Baltimore; 54.6 per cent of both the Mongol and control fathers were born in Baltimore ($\chi^2 = 1.54$, not statistically significant). In addition, there were no other significant differences in areas of birth—either within or outside the United States.

The length of time spent in Baltimore prior to the birth of the index child was very similar for both groups of parents and is summarized in Table II. Mongol and control mothers numbering respectively, 56.5 per cent and 57.0 per cent and 50.5 per cent and 53.7 per cent of the Mongol and control fathers had spent their entire lives in Metropolitan Baltimore, either starting from birth or prior to age 15. There were no significant differences, for residential history between the cases and controls. Furthermore, there were no significant differences in the total number of years spent in other major areas of the United States prior to the birth of the index child.

Analysis of the type of parental residence during the five years prior to the index child's birth demonstrated that there was no concentration of parents either in the rural or urban areas during this period. Ninety-three and one-half per cent of the Mongol mothers and 92.1 per cent of the control mothers lived in cities during this time period, while 89.7 per cent of the Mongol fathers, and 89.0 per cent of the control fathers were in this same category.

There were also no important differences in the kind of construction materials present in the parental dwellings during this period. Brick, stone, wood or combination type dwellings were reported with similar frequency.

II. *Hospitalization History*

Since a separate evaluation was made of radiation exposure occurring only in Baltimore hospitals, it was essential to determine whether differences existed in the frequency of hospital attendance. Sixty-one and one-

[5] All percentage distributions are calculated on the basis of total known positive or negative responses, after "Unknowns" have been subtracted.

TABLE II

Residential History in Baltimore Prior to Birth of Index Child

Type of Residence	Mothers				Fathers			
	Mongols		Controls		Mongols		Controls	
	No.	%	No.	%	No.	%	No.	%
Lifetime residence since birth	106	49.1	98	45.4	101	46.8	105	48.6
Lifetime residence since 15 yrs. or younger	16	7.4	25	11.6	8	3.7	11	5.1
Not lifetime residence	93	43.0	91	42.1	99	45.8	97	44.9
Total reported	215	99.5	214	99.1	208	96.3	213	98.6
Unknown	1	.5	2	.9	8	3.7	3	1.4
Total	216		216		216		216	

half and 62.8 per cent of the Mongol and control mothers plus 30.3 per cent and 30.8 per cent of the Mongol and control fathers respectively, reported that all their hospitalizations had occurred in Baltimore. Thirty-five and seven tenths per cent and 34.9 per cent of the Mongol and control mothers and 21.6 per cent and 22.9 per cent of the Mongol and control fathers respectively reported hospitalizations to have occurred either in Baltimore or outside of the city. A larger number of hospitalizations outside the city were reported by the fathers, mainly due to illnesses which occurred during military service.

Because the hospital records were searched independently and irrespective of the data acquired on interview, the assessment of the accuracy of the reporting and the success of locating medical records was not available until completion of the study. Analysis then revealed no significant differences between the Mongol and control parents with respect to either the over or under-reporting of hospitalizations (Table III). The medical hospitalizations were reported with most accuracy and as a relative measure, hospitalizations for tonsillectomy and/or adenoidectomy were reported with least reliability. The accuracy of reporting, therefore, was much greater among mothers than fathers, but case and control parents were practically identical. A total of 24 hospitalizations were found on medical records that were not reported by Mongol mothers as compared to 15 for control mothers. Similarly, the Mongol fathers failed to report nine hospitalizations and the controls seven.

III. *Radiation Exposure—Place of Occurrence*

Distribution of the parents according to the source of the radiation exposures reported on interview are shown in Table IV. There was, again,

TABLE III

Summary of Baltimore Hospitalizations Reported on Interview and Per Cent Verified as Correct on Hospital Records

Maternal or Paternal Age at Interview	Number of Hospitalizations											
	Mothers						Fathers					
	Interview		Verified on Hosp. Records				Interview		Verified on Hosp. Records			
	Mong.	Control	Mongol		Control		Mong.	Control	Mongol		Control	
	No.	No.	No.	%	No.	%	No.	No.	No.	%	No.	%
20–24	5	8	5	100.0	8	100.0	1	—	—	—	—	—
25–29	31	33	23	74.2	25	75.8	3	2	3	100.0	1	50.0
30–34	90	86	82	91.1	70	81.4	24	9	7	29.2	6	66.7
35–39	116	78	95	81.9	63	80.8	31	28	14	45.2	17	60.7
40–44	138	146	95	68.8	113	77.4	27	27	16	59.3	13	48.1
45–49	208	222	168	80.8	168	75.7	27	26	13	48.1	14	53.8
50–54	91	101	73	80.2	57	56.4	20	28	12	60.0	14	50.0
55 or more	39	21	23	59.0	16	76.2	20	21	11	55.0	8	38.1
Deceased	10	—	4	40.0	—	—	2	4	3	150.0	5	125.0
No interview	—	—	2	—	—	—	—	—	—	—	—	—
Total	728	695	570	78.3	520	74.8	155	145	79	51.0	78	53.8

TABLE IV

History of Lifetime Radiation Exposure—Place of Occurrence Taken from Interview

Place of Total Exposure	Mothers				Fathers			
	Mongols		Controls		Mongols		Controls	
	No.	%	No.	%	No.	%	No.	%
All in Balto. hospitals	47	23.9	45	22.2	23	12.8	26	13.3
Balto. hosps. plus Balto. private physicians	28	14.2	36	17.7	31	17.3	32	16.3
All from Balto. private physicians	40	20.3	35	17.2	23	12.8	35	17.9
All in Balto. and outside hospitals	4	2.0	2	1.0	13	7.3	13	6.6
All in outside hospitals*	7	3.6	9	4.4	25	14.0	28	14.3
Other combinations	9	4.5	7	3.5	19	10.7	19	9.7
Total exposed	135		134		134		153	
No exposure reported	62	31.5	69	34.0	45	25.1	43	21.9
Total known	197		203		179		196	
Unknown	19	8.8	13	6.0	37	17.1	20	9.3
Total	216		216		216		216	

* Outside of Baltimore City.

great similarity between the Mongol and control parents with respect to the number of parents reporting that all radiation exposures occurred in Baltimore hospitals. Because of the magnitude of the task, there was no independent study or verification of sources other than the Baltimore hospitals, and analysis in these cases was confined to the interview data.

IV. *Description of Radiation Exposure*

The history of irradiation as summarized from the interview and medical records is divided into the following categories: 1) diagnostic radiation excluding fluoroscopy, 2) fluoroscopic exposure, 3) radiation for therapy and 4) occupational contact.

The medical radiation data include the exposures from contact with physicians of medicine only and do not include irradiation from dentists, other types of physicians, or from use of shoe fitting apparatus.

Since analysis of hospital records was limited to Baltimore hospitals, the total exposures reported on interview for each kind of radiation is considerably more, for each group, than was found in the medical records alone. (Most of the total radiation exposure occurred at places other than the Baltimore hospitals).

A. *Diagnostic Radiation*

A summary of the total x-ray exposure for diagnostic purposes prior to the index case birth (excluding fluoroscopy) is shown in Table V. The data, as shown, include the total number of individual sessions at which diagnostic x-rays were taken rather than the actual number of x-ray films exposed; the precise number of exposures per session was impossible to estimate in a retrospective study, but the total number of sessions reported is assumed to represent at least one x-ray film exposure. The number of occasions x-rays were taken prior to the birth of the index child was totaled separately from both the interview and hospital records. There was a slight excess of total exposures for the Mongol mothers recorded at interview and also independently, from hospital records. However, in neither case is the difference statistically significant ($\chi^2 = 1.54$ and $\chi^2 = .88$ respectively). In addition, the total diagnostic exposure for the Mongol and control fathers is practically identical and, again, there is close agreement between the interview and medical records. It should be understood, as already explained, that only a portion of the diagnostic radiation exposure occurred at Baltimore hospitals. Therefore, the diagnostic radiation exposure is considerably less than that reported on interview and must be considered as a similar, but separate measure of exposure.

The total diagnostic exposure (excluding fluoroscopy) was further ana-

TABLE V

Total Number of X-rays or Other Radiation for Diagnosis Prior to Birth of the Index Child

(Excluding Fluoroscopy)

No. Times	Interview Data								Hospital Records							
	Mothers				Fathers				Mothers				Fathers			
	Mongols		Controls		Mongols		Controls		Mongols		Controls		Mongols		Controls	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1	45	22.0	40	19.3	38	20.1	32	15.7	31	14.4	22	10.2	12	5.7	14	6.5
2	12	5.9	15	7.3	16	8.5	17	8.3	12	5.6	11	5.0	9	4.3	8	3.7
3	10	4.9	5	2.4	8	4.2	10	4.9	3	1.4	2	.9	4	1.9	7	3.3
4	5	2.5	1	.5	6	3.2	8	3.9	2	.9	5	2.3	4	1.9	3	1.4
5 or more	5	2.5	5	2.4	14	7.4	14	6.9	5	2.3	5	2.4	3	1.4	2	.9
Total positive	77		66		82		81		53		45		32		34	
None reported	127	62.2	141	68.1	107	56.6	123	60.3	162	75.4	171	79.2	179	84.8	181	84.2
Total known	204		207		189		204		215		216		211		215	
Unknown	12	5.6	9	4.2	27	12.5	12	5.6	1	.5	—	—	5	2.3	1	.5
Total	216		216		216		216		216		216		216		216	

Fathers $\chi^2 = 1.54$, $P = > .20$ 1 D.F.

Mothers $\chi^2 = .88$ $P > .30$ 1 D.F.

lyzed according to the type of the x-ray procedure. The results of parental exposure from abdominal and/or pelvic x-rays are shown in Table VI. There was a greater amount of abdominal and/or pelvic exposures reported on interview for both the mothers and the fathers of Mongols as compared with control parents. However, the differences cannot be considered as significant ($P \cong .10$). Because analysis of the total diagnostic exposures revealed little difference between the cases and controls with respect to multiple exposure episodes, statistical evaluation of the remaining types was based on the total of one or more exposure episodes. Table VII summarizes the results of enumeration of each type of exposure with the χ^2 value based on the total of one or more episodes prior to the birth of the index child. Where the difference was very small, no χ^2 value was calculated. Because of both the scarcity of positive results and the failure to reach higher probability levels, the results in this category of exposure cannot be considered to be beyond the limits of chance.

In all cases, the exposures were spread over a period of one to 20 years without any concentration in the years immediately preceding the birth. In addition, the number of exposures tended to increase with parental age, but there were no major differences between the two groups.

Diagnostic x-ray exposure following the birth of the index child was also studied, using only the interview data. There was no difference in the total number of exposure-episodes for either mothers or fathers. There were also no significant differences found when the total exposure following the index child's birth was broken down by individual kinds of x-rays.

B. *Fluoroscopic Exposure*

The total maternal fluoroscopic exposures reported on interview are summarized in Table VIII and tabulated according to the number of sessions and maternal age at the time of birth of the child; 17.7 per cent of the Mongol mothers had one or more fluoroscopic examinations prior to birth of the index case, as compared to only 8.1 per cent of the controls. This difference is significant at less than the 1 per cent level ($\chi^2 = 8.25$, $P < .01$). As expected, the number of exposures increased with advancing maternal age. However, even though the mothers were matched for maternal age, 58.3 per cent of the Mongol mothers reporting fluoroscopy were over 35 years at the time of the case birth, as compared to 43.8 per cent of the control mothers.

The body area exposed during fluoroscopy as related by the mothers is shown in Table IX. The larger amount of fluoroscopy in the Mongol mothers results from the combined increase of chest, abdominal and "other types" of exposure. The number of Mongol mothers reporting ex-

TABLE VI

Total Diagnostic Abdominal and/or Pelvic X-rays Prior to Birth of Index Child

No. of Instances	Mothers								Fathers							
	Interview				Hospital Records				Interview				Hospital Records			
	Mongols		Controls		Mongols		Controls		Mongols		Controls		Mongols		Controls	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1	28	13.2	20	9.4	23	10.6	16	7.4	9	4.4	6	2.8	4	1.9	5	2.3
2	4	1.9	2	.9	1	.5	3	1.4	4	2.0	1	.5	1	.5	2	.9
3 or more	3	1.4	1	.5	1	.5	2	.9	1	.5	—	—	—	—	1	.5
Total positive	35		23		25		21		14		7		5		8	
None reported	177	83.5	190	89.2	191	88.4	195	90.3	190	93.1	206	96.7	206	97.6	208	96.3
Total known	212		213		216		216		204		213		211		216	
Unknown	4	1.9	3	1.4	—	—	—	—	12	5.5	3	1.4	5	2.3	—	—
Total	216		216		216		216		216		216		216		216	
	$\chi^2 = 2.91$ $P > .05$ (Interview)				$\chi^2 = .38$ $P > .50$ (Hospital Records)				$\chi^2 = 2.76$ $P > .05$ (Interview)				$\chi^2 = .65$ $P > .30$ (Hospital Records)			

TABLE VII

Summary of Diagnostic X-ray Exposure Prior to Birth of Index Child
(Fluoroscopy Excluded)

Type of Diagnostic X-ray	Mothers				Fathers			
	Interview		Hospital Records		Interview		Hospital Records	
	χ^2	P	χ^2	P	χ^2	P	χ^2	P
Chest X-ray	N.D.*		.82	>.30	N.D.		N.D.	
Gallbladder series	.225	>.50	N.D.		N.D.		5.12	<.05
Kidney, including I.V.P.	N.D.		N.D.		.50	>.30	N.D.	
Abdominal, including G.I. series	N.D.		N.D.		1.18	>.20	N.D.	
Head	N.D.		N.D.		.69	>.30	N.D.	
Spine	−4.81	<.05	N.D.		N.D.		1.36	>.20
Arm &/or leg	.40	>.50	3.88	<.05	.82	>.30	−1.46	>.20
Other organs	N.D.		N.D.		N.D.		N.D.	

Note: (−) (Minus sign) = greater exposure for controls.
* N.D. = No Difference.

TABLE VIII

Total Interview Data for Maternal Fluoroscopic Exposure Prior to Birth of the Index Child by Maternal Age at Birth of IC and Number of Fluoroscopic Sessions

Maternal Age at IC Birth	Number of Sessions													
	Mongols							Controls						
	1	2 or more	Total Positive	None Reported	Total Known	Unk.	Total	1	2 or more	Total Positive	None Reported	Total Known	Unk.	Total
19 or less	—	—	—	6	6	—	6	—	—	—	6	6	—	6
20–24	3	—	3	28	31	3	34	2	1	3	29	32	1	33
25–29	3	—	3	26	29	1	30	1	—	1	29	30	2	32
30–34	9	—	9	34	43	4	47	5	—	5	38	43	5	48
35–39	13	1	14	45	59	4	63	3	2	5	50	55	7	62
40–44	3	3	6	27	33	1	34	2	—	2	30	32	3	35
45 or more	1	—	1	1	2	—	2	—	—	—	—	—	—	—
Total	32	4	36	167	203	13	216	13	3	16	182	198	18	216
% of known	15.8	1.9	17.7	82.3		6.0		6.6	1.5	8.1	91.9		8.3	

$\chi^2 = 8.25$, $P = <.01$.

posure of the chest or abdomen is almost twice that of the controls. (Chest $\chi^2 = 2.56$, Abdomen $\chi^2 = 2.25$, Other $\chi^2 = 2.69$.)

Because only a small amount of the total radiation exposure occurred in the Baltimore hospitals (the majority from private physicians and other sources), the number of fluoroscopic episodes in these hospitals was very

TABLE IX

Interview Data for Fluoroscopic Exposure Prior to Birth of Index Child by Type and Number of Sessions

Number of Sessions	Mothers											
	Mongols						Controls					
	Chest		Abdomen		Other		Chest		Abdomen		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1	20	9.8	13	6.3	6	2.9	8	4.0	7	3.5	2	1.0
2 or more	1	.5	1	.5	1	.5	4	2.0	—	—	—	—
Total positive	21		14		7		12		7		2	
None reported	183	89.7	191	93.2	198	96.6	188	94.0	193	96.5	198	99.0
Total known	204		205		205		200		200		200	
Unknown	12	5.6	11	5.1	11	5.1	16	7.4	16	7.4	16	7.4
Total	216		216		216		216		216		216	

small, and not amenable to statistical analysis. However, the discovery of the small number of exposures after searching the hospital records was verification for the small number of Baltimore hospital exposures reported by the mothers on interview. From medical records, there were reports of only one Mongol and three control mothers with a history of bona fide fluoroscopy prior to birth of the index case. Therefore, most of the excess of fluoroscopy in the Mongol mothers can be attributed to sources other than the Baltimore hospitals. In contrast, the control mothers reported more fluoroscopic procedures following the birth of the index child than the Mongol mothers. However the difference was not statistically significant ($\chi^2 = 2.61$, $P > .10$).

The fluoroscopic history of case and control fathers, both prior to and after the birth of the index child, was strikingly similar. On interview, 7.9 per cent and 8.8 per cent of the Mongol fathers reported chest and abdominal fluoroscopic procedures respectively, while 7.8 per cent and 7.9 per cent of the control fathers reported chest and abdominal exposures before the birth of the index case. The number of exposures for fathers found on medical records for the same time period was also very small and not significant.

C. *Therapeutic Radiation*

The data on maternal and paternal therapeutic radiation exposure are presented in Table X. Of the mothers of Mongols, 14.5 per cent reported

TABLE X

Therapeutic Radiation Exposure Prior to Birth of Index Child Interview Data

Number of Parents Having One or More Exposures

Condition or Area	Prior to Index Child								Post Index Child							
	Mothers				Fathers				Mothers				Fathers			
	Mongols		Controls		Mongols		Controls		Mongols		Controls		Mongols		Controls	
Skin	19		5		9		7		2		2		3		2	
Warts &/or birth marks	4		2		1		1		2		1		—		1	
Tumors	1		—		2		2		3		2		—		3	
Sinus &/or adenoids	1		1		1		1		—		2		1		—	
Bursitis	2		—		1		2		3		—		3		5	
Arthritis	1		1		—		—		1		2		—		—	
Menstrual or reproductive disorders	—		1		—		—		2		—		—		1	
Thyroid	—		—		—		—		1		1		—		—	
Polycythemia	—		—		—		—		—		—		—		—	
Other	3		1		2		3		1		—		1		2	
Total positive & percent	31	14.5	11	5.1	16	7.8	16	7.5	15	7.0	10	4.7	8	3.8	14	6.5
None reported & percent	183	85.5	203	94.9	190	92.2	198	92.5	199	93.0	205	95.3	200	96.2	200	93.5
Total known	214		214		206		214		214		215		208		214	
Unknown	2	.9	2	.9	10	4.6	2	.9	2	.9	1	.5	8	3.7	2	.9
Total	216		216		216		216		216		216		216		216	

Mothers Prior

$\chi^2 = 10.54,\ P = <.01$

one or more therapeutic exposures as compared to only 5.1 per cent of the control mothers—a three-fold increase. No differences were noted for the fathers. The increased Mongol maternal exposure constitutes a highly significant difference ($\chi^2 = 10.54$, $P < .01$). The major portion of this difference is contributed by the large number of exposures to the skin reported by the Mongol mothers; 8.8 per cent of the Mongol mothers received skin irradiation and only 2.3 per cent of the controls—a difference that is also significant ($\chi^2 = 8.64$, $P < .01$). Of the 19 Mongol mothers who received skin therapy, six were irradiated for acne, two for eczema, five for various other skin conditions, and six for unspecified diseases. Neither acne nor eczema were reported as a reason for skin irradiation by the control mothers. There were also six control mothers who did not specify the kind of disease for which they were irradiated.

No important differences were found in the time relationship of the exposure to the birth of the index child; most of the skin irradiation to the Mongol mothers occurred more than eight years before the birth of the child.

The number of therapeutic exposures listed in the medical records were extremely few and were not useful for analysis.

The Mongol mothers were also found to have a slight, but not significant excess of therapeutic exposures following the birth of the child. The fathers again failed to reveal significant differences for therapeutic exposure.

D. *Occupational Exposure*

The occupational histories of the parents were scrutinized for indications of possible exposure to radiation or other energy sources. Seven and nine-tenths per cent of the Mongol mothers and 3.3 per cent of the control mothers worked in a professional or technical capacity in medical fields. This difference is significant at the 5 per cent level. Mongol mothers numbering 82.4 per cent were employed for more than one year in medical fields. Eight Mongol mothers and three control mothers gave actual histories of x-ray and/or fluoroscopic exposures in all types of occupations prior to the index child.

The experience of the fathers prior to the index case in various occupations was very similar, except for an excess of military service for the fathers of children with Mongolism. There were only four fathers from each group who had been involved in professional or technical work in the medical fields prior to the child.

Because of extensive history of paternal involvement in the armed services, an analysis of military experience was carried out. This revealed that 63.1 per cent of the Mongol fathers as compared to 56.6 per cent of the

control fathers had service experience prior to the birth of the index child: the difference is not statistically significant. Eleven and one-half per cent of the Mongol fathers and 7.9 per cent of the control fathers were in military service within two years prior to the conception of the index child. Only two Mongol and two control fathers had military duty following the conception of the index child. One hundred and four Mongol fathers and 100 control fathers had their military experience more than two years prior to the conception of the index child. There was an increased but not statistically significant number of Mongol fathers in the Army during this military service.

There were no important differences in the professional or industrial radiation exposures for the fathers prior to the birth of the index child.

As an additional source of radiation energy, though non-ionizing in nature, a history of radar exposure was elicited from the fathers. A significantly increased amount of radar exposure was obtained from the Mongol fathers. Eighteen, or 8.7 per cent, of the fathers of children with Mongolism and seven, or 3.3 per cent, of the fathers of controls reported intimate contact with radar both in and outside of the armed forces ($\chi^2 = 5.37$, $P \cong .02$). The military radar contact occurred when the father was either a radar technician or radar operator. The increase in military radar exposure in the Mongol fathers is supported by their histories of increased military service.

E. *Summary of Exposure*

A summary tabulation and analysis of the parental diagnostic, therapeutic and fluoroscopic exposure is presented in Table XI. Of those parents with definite "yes" or "no" answers for radiation exposure, 50 per cent of the Mongol mothers reported "no radiation" as compared to 59.9 per cent of the control mothers. This difference is significant ($\chi^2 = 4.13$, $P < .05$). Hospital record analysis revealed that 72.7 per cent of the Mongol mothers had no radiation whatsoever, as compared to 78.2 per cent of the control mothers ($\chi^2 = 1.80$, $P > .10$). As shown in previous tables, the increased exposure of the Mongol mothers, as reported on interview, is mainly a result of fluoroscopic and therapeutic radiation. Thirteen Mongol mothers and only two control mothers reported a combination of one or more each of diagnostic, fluoroscopic and therapeutic exposures—a difference which is significant ($\chi^2 = 8.30$, $P < .01$). The summary of hospital radiation experience again demonstrates the sparse amount of fluoroscopic or therapeutic radiations recorded. However, an increased amount of diagnostic exposure for the Mongol mothers is evident, though not statistically significant ($\chi^2 = 2.86$, $P \cong .10$).

The Mongol fathers also demonstrated a slight total increase of radia-

TABLE XI

Summary of Parental Diagnostic, Fluoroscopic, & Therapeutic Radiation (One or More Exposures) Interview and Medical Records Prior to Birth of the Index Child

Type of Exposure	Mothers				Fathers			
	Mongols		Controls		Mongols		Controls	
	No.	%	No.	%	No.	%	No.	%
Interview								
No Radiation	104	50.0	124	59.9	86	43.7	102	50.0
Radiation								
Diagnostic only	50	24.0	56	27.1	62	31.5	52	25.5
Fluoroscopic only	10	4.8	7	3.4	11	5.6	11	5.4
Therapeutic only	8	3.3	3	1.4	4	2.0	4	1.9
Diagnostic & fluoroscopic	14	6.7	8	3.9	17	8.6	21	10.3
Diagnostic & therapeutic	7	3.4	6	2.9	11	5.6	10	4.9
Fluoro. & therapeutic	2	1.0	1	.5	2	1.0	2	1.0
Diag., fluoro., & therapeutic	13	6.3	2	.9	4	2.0	2	1.0
Total known	208		207		197		204	
Unknown	8	3.7	9	4.2	19	8.8	12	5.6
Total	216		216		216		216	
Hospital Records								
No radiation	157	72.7	169	78.2	184	85.6	182	84.2
Radiation								
Diagnostic only	59	27.3	44	20.4	31	14.4	31	14.4
Other types	—	—	3	1.4	—	—	3	1.4
Total known	216		216		215		216	
Unknown	—	—	—	—	1	.5	—	—
Total	216		216		216		216	

tion exposure. Of those with a definitive interview response, 43.7 per cent of the Mongol fathers reported "no radiation" as compared to 50.0 per cent of the control fathers. This difference, however, is not significant ($\chi^2 = 1.62$, $P > .20$). The paternal hospital records, in contrast, are strikingly similar for radiation exposure. An almost identical number of both Mongol and control fathers were found to have no radiation exposure whatsoever.

DISCUSSION

The findings of several studies designed to determine the relationship of parental radiation exposure and the occurrence of Mongolism are somewhat contradictory. Uchida and Curtis (24) in 1961, reported a striking relationship between radiation and Mongolism—that 28 per cent of a group of 81 mothers of Mongols were exposed to four or more abdominal x-rays or fluoroscopies prior to the Mongol's birth, as compared to 4 per cent of mothers of cleft lip children and 14 per cent of neighbors. In contrast, Lunn (25) reported no significant difference between the x-ray exposure of the mothers of Mongols and controls; similarly, Carter *et al.* (26) found no differences in the maternal abdominal radiation prior to conception in a study based on interview data, and Schull and Neel (27) reported no association in the data based on offspring of survivors of atomic bomb explosions in Hiroshima and Nagasaki. However, except for the Japanese data which represent a unique type of radiation exposure, each of these studies is concerned primarily with diagnostic radiation experience, or has not separated out diagnostic and other types of radiation. Furthermore, each study has limitations of a methodological nature.

In the present study, attempts were made to eliminate or control those factors which might involve bias in a retrospective study as well as to evaluate various types of maternal and paternal exposure; and there appears to be a definite association between maternal exposure to ionizing radiation and Mongolism. A sample derived from almost all of the cases of Mongolism born in Baltimore between 1946 and 1962 was obtained, and the diagnosis in each case included was verified either by physical examination or on the basis of standardized criteria from reliable medical records. To the Mongols determined eligible for inclusion in the study, controls were matched with regard to sex, race, date of birth, hospital of birth and maternal age at time of birth of the child. On interview an objective questioning procedure was used with equal emphasis on each sibling and pregnancy in each family.

The very close matching of maternal age (the mean age of mothers of Mongols was 32.6 as compared to 32.5 for the control mothers) eliminated

the possibility that any greater radiation exposure in the mothers of Mongols might be a function of a greater number of years at risk for these mothers as compared to the mothers of the controls. The absence of any significant paternal age effect in Mongolism, as shown previously, made it unnecessary to correct for paternal age in evaluating the data on the father (28).

A striking similarity between the parents of Mongols and of controls demonstrated from the study of several other variables lends further emphasis to the observed radiation differences. Since both groups of parents spent very similar amounts of time in Baltimore, and other geographical areas, prior to the birth of the index child, differences in proximity to institutions where radiation was easily accessible, could not account for the observations. In addition, the uniformity of residential history tended to eliminate other local environmental factors, including background radiation, from having an important role in the etiology of this condition.

Moreover, the close agreement between the parents of both groups regarding the number of Baltimore hospitalizations reported, tended to exclude the biased recollection of serious illnesses as an explanation for differences in radiation exposure in this study.

By far the best measure of the accuracy of the interview data and the absence of any significant retrospective bias from the Mongol parents clearly came from the actual verification of the hospitalization history. There were no significant differences between the Mongol and control parents with respect to either the over or under-reporting of hospitalizations. In fact, the Mongol parents *forgot* to report more hospitalizations that had actually occurred than did the controls. Even in the older age groups, there was no memory advantage demonstrated for the parents of Mongols, further eliminating any differences in recall, as is sometimes suggested as a source of bias in interview studies.

Finally, there was no evidence of an increased willingness of the parents of the Mongols to cooperate in the study since the refusal rates were very similar in both groups. When a refusal did occur, the matched case or control was always eliminated.

From this preliminary examination to ascertain the validity of the collected data and evaluate any possible bias, it therefore seems reasonable to assume that whatever relationships are observed in this case-control study would not result from any artifact introduced through the sources, selection, completeness or mode of collection of the data.

The tabulated results already described in detail, clearly indicate that the mothers of Mongoloid children received significantly more radiation (in particular, fluoroscopy and therapeutic radiation) than the mothers of

the control children. In fact, in the case of combined irradiation from one or more diagnostic, fluoroscopic and therapeutic sources, mothers of Mongols had seven times as many radiographic procedures as the control mothers. This highly significant difference represents an accumulated exposure prior to the index child from various radiation sources. Moreover, significantly fewer mothers of Mongols than mothers of controls failed to receive any radiation prior to the index child.

Because the actual date of conception was impossible to determine, the parents were questioned and medical records searched for the entire period "prior to the *birth* of the index child." However, there was very little radiation exposure reported around the time of conception and practically no exposure during intrauterine life.

The observation that the major maternal radiation exposure occurred over many years prior to the index child's birth is consistent with the views concerning cumulative radiation damage to genetic material. Since, unlike in the male, the full complement of germ cells is present in human females from the time of birth, they are susceptible to repetitive damage either from the same or different environmental sources. The association of Mongolism with advanced maternal age adds credence to this cumulative radiation effect.

Most noteworthy is the fact *that the substantially greater* exposure to the mothers of Mongols was contributed by those radiation sources expected to provide large doses. Although dosimetry is lacking in this study, a description of the type of exposure is valuable and useful for relative dosages within wide ranges. While there was a greater total diagnostic exposure demonstrated for the mothers of the Mongols, the difference was not statistically significant. The major difference came from fluoroscopic and therapeutic sources. A significantly greater number of fluoroscopic sessions was reported by the Mongol mothers, with fluoroscopies of the abdomen and chest contributing the major excess. The duration of each exposure was impossible to determine, and the number of bona fide fluoroscopic procedures found on the medical records was too small to be useful for comparison.

Therapeutic radiation for a variety of conditions was partly responsible for the greater exposure in the mothers of Mongols, with therapy many years prior to the index child's birth for acne, eczema and other dermatologic conditions contributing heavily to the significant differences between mothers of Mongols and mothers of controls. Again, although no dosimetry was available, it is recognized that therapeutic irradiation—especially from sources used in past years—produces high exposure with scatter over much of the body area.

Of additional interest was the observation that significantly more mothers of Mongols were employed in professional or technical occupations in the medical field prior to the birth of the index child. Although no greater radiation exposure was reported by these mothers, the possibility of inapparent or accidental exposure is likely.

The radiation history of the fathers of the Mongols provides a marked contrast to that of the mothers. There was striking similarity and in some cases almost identical medical radiation exposure reported by the fathers of Mongols and of the controls. Only minor differences were reported for diagnostic, fluoroscopic and therapeutic exposures. Except for more radar exposure to the fathers of Mongols along with more military service where this exposure occurred, there was no evidence for any association between paternal irradiation and Mongolism. Moreover there was no indication of any increased exposure of the fathers of Mongols in the period around the time of conception of the abnormal child. This similarity of the radiation exposure of fathers of Mongols and of controls is also consistent with the failure to demonstrate a correlation between Mongolism and paternal age and provides additional evidence against the presence of any bias in reporting of retrospective data in this study (28).

Ever since the discovery and confirmation of the existence of a chromosomal abnormality in Mongolism (29–33) it has been clear that whatever environmental agents may lead to that chromosomal defect must act on parental germ cells prior to conception or, in rare cases, on zygotes not later than several days after fertilization.

It is well established on the basis of evidence in experimental organisms that radiation can cause non-disjunction (1–5, 34–39) as well as chromosomal breaks leading to various types of aberrations (38–42). In every plant and animal species adequately investigated, ionizing radiation has proven to be mutagenic with no known threshold dose in studies that have carried the total dosage down to 5 r (38–49).

While there are no direct experimental data relating either specifically to the radiosensitivity of human female germ cells in the dictyotene stage or specifically to non-disjunctional events in human females, there now exists not only substantial support from a wide range of other organisms, but also a growing body of data from mammals concerning the various types of damage to germ cells (37, 53–62). Rapidly accumulating data have also demonstrated chromosomal aberrations in the somatic cells of humans following exposure to ionizing radiation. Tough *et al.* (6) reported a 20 per cent increase in the number of circulating leukocytes with 47 chromosomes 24 hours after x-ray treatment of a patient with ankylosing spondylitis. Similarly, extensive observations by Buckton *et al.* (7) on blood

cultures from 58 patients with ankylosing spondylitis treated with one course of x-ray therapy to the spine showed chromosomal damage with persistence of some abnormalities up to 20 years after irradiation. Furthermore the frequency of the chromosomal abnormalities increased significantly in subjects irradiated at age 35 or over. Bender and Gooch (8) reported chromosomal abnormalities present in a small group of men after they were irradiated with gamma and fission neutron irradiation.

Chromosomal aberrations have been reported following lower dosage diagnostic radiation. Stewart and Sanderson (9) and Conen *et al.* (10) described the appearance of chromosomal defects in subjects exposed to as little as 0.8 rads. Bloom and Tjio (11) studied the pre and post-abdominal fluoroscopy, or fluoroscopy with cardiac catheterization and reported aberrations in each of five patients exposed to between 12 and 35 r following abdominal fluoroscopy.

It is therefore not only likely but probable that chromosomal abnormalities occur in human germinal tissue exposed to therapeutic and diagnostic levels of radiation. On the basis of known patterns of human gametogenesis, the radiosensitivity of human tissues, and the genetic effects of radiation in experimental animals there appears to be remarkable consistency between the findings of this study and what might be expected biologically.

Increased radiosensitivity may also contribute to the maternal age effect. Evidence from experimental organisms indicates that with increasing age there is increased susceptibility to chromosomal damage from radiation and other agents (36, 38, 63). Even more important have been Russell's recent observations of age associated increased radiosensitivity of oocytes in female mammals (61).

Finally, the only truly puzzling association is the suggested relationship between Mongolism and paternal radar exposure. Recent studies have revealed that radar, a form of microwave energy, can cause tissue damage in humans and laboratory animals (64, 66). In addition, microwave radiation has been reported to have a deleterious effect on rat testis (67).

The increased radar exposure of fathers of Mongols as compared with controls raises the question as to whether ionizing radiation, in addition to the known heating effect, may be involved in radar operations. Since, however, no greater exposure to medical radiation was observed among fathers of Mongols as compared to fathers of controls, radar, under special circumstances, must involve some unique and potent effect that overcomes the male advantage of continuous spermatogenesis. One can only speculate concerning possible mechanisms, but the association between Mongolism and radar exposure deserves further investigation.

The acknowledged association of Mongolism and leukemia (12–14) and radiation and leukemia (15–21) is additional evidence consistent with the hypothesis that radiation is of etiological importance in Mongolism.

The conclusion derived from the present study is that Mongolism is statistically associated with maternal radiation. The likelihood that the radiation association is a causal relationship is considerably enhanced by the evidence—experimental and other kinds—which has already been reviewed. In addition comparisons of several other characteristics, including medical and surgical histories, of the mothers of Mongols and controls did not reveal any differences, except for a higher frequency of divorce among Mongol mothers. These additional results will be reported in detail later. It should therefore be emphasized that although a causal interpretation does not mean that radiation must be implicated in every case, the results do suggest that certain physical energy sources, such as ionizing radiation, are involved in the pathogenesis of some cases of Mongolism.

SUMMARY

As part of an epidemiologic study in Baltimore Maryland, a population of parents of both Mongoloid and control children was evaluated for exposure to various types of ionizing radiation. Utilizing interview technique and medical record analysis, the study demonstrated a statistical association between maternal radiation exposure and Mongolism. The mothers of the Mongoloid children were found to have a significantly increased exposure to both fluoroscopic and therapeutic irradiation prior to the birth of the index child.

In contrast, there were no significant differences in ionizing radiation exposure found in the fathers of the Mongol and control children. However, a surprising increase in radar exposure was discovered in a significant number of fathers of the Mongol cases.

These results suggest that maternal ionizing radiation exposure may be one etiological factor responsible for some cases of Mongolism. It is emphasized, however, that ionizing radiation may be only one of several important factors in the pathogenesis of the condition.

REFERENCES

1. Mavor, J. W.: The production of non-disjunction by x-rays. Science, 1922, **55:** 295.
2. Demerec, M. and Farrow, J. G.: Non-disjunction of the X-chromosome in Drosophilia Virilis. Proc. Nat. Acad. Sci., 1930, **16:** 707.
3. Demerec, M.: Relation between the x-ray dosage and the frequency of primary non-disjunctions of the X-chromosomes in Drosophilia Virilis. Proc. Nat. Acad. Sci., 1930, **16:** 711.

4. ANDERSON, E. G.: The constitution of primary exceptions obtained after x-ray treatment of Drosophila. Genetics, 1931, **16:** 386.
5. SAVHAGEN, R.: The effect of oxygen concentration on the frequency of induced XO males and non-disjunction females after irradiation of Drosophila males. Hereditas, 1961, **47**(2): 163.
6. TOUGH, I. M., BUCKTON, K. E., BAIKIE, A. G. AND COURT-BROWN, W. M.: X-ray induced chromosome damage in man. Lancet, 1960, **II:** 849.
7. BUCKTON, K. E., JACOBS, P. A., COURT-BROWN, W. M. AND DOLL, R.: Study of chromosomal damage persisting after x-ray therapy for ankylosing spondylitis. Lancet, 1962, **II:** 676.
8. BENDER, M. A. AND GOOCH, P. C.: Persistent chromosome aberrations in irradiated human subjects. Radiat. Res., 1963, **18:** 389.
9. STEWART, J. S. AND SANDERSON, A. R.: Chromosomal aberration after diagnostic x-irradiation. Lancet, 1961, **I:** 978.
10. CONEN, P. E., BELL, A. G. AND ASPEN, N.: Chromosomal aberrations in infant following the use of diagnostic x-rays. Pediatrics, 1963, **31:** 72, Part 1.
11. BLOOM, A. D. AND TJIO, J. H. In vivo effects of diagnostic X-irradiations on human chromosomes. New Eng. J. Med., 1964, **270:** 1341.
12. KRIVIT, W. AND GOOD, R. A.: Simultaneous occurrence of mongolism and leukemia. Report of a nationwide survey. J. Dis. Child., 1957, **94:** 289.
13. STEWART, A., WEBB, J. AND HEWITT, D.: Survey of childhood malignancies. Brit. Med. J., 1958, **I:** 1495.
14. WALD, N., BORGES, W. H., LI, C. C., TURNER, J. H. AND HARNOIS, M. C.: Leukemia associated with Mongolism. Lancet, 1961, **I:** 1228.
15. LONGE, R. D., MOLONEY, W. C. AND YAMOWAKI, T. Leukemia in atomic bomb survivors. I. General observations. Blood, 1954, **9:** 574.
16. FOLLEY, J. H., BORGES, W. AND YAMOWAKI, T.: Incidence of leukemia in survivors of atomic bomb in Hiroshima and Nagasaki, Japan. Amer. J. Med., 1952, **13:** 311.
17. BRILL, A. B., TOMONOZA, M. AND HEYSSEL, R. M.: Leukemia in man following exposure to ionizing radiation. Summary of findings in Hiroshima and Nagasaki, and comparison with other human experience. Ann. Intern. Med., 1962, **56:** 590.
18. LEWIS, E. B.: Leukemia, multiple myeloma and aplastic anemia in American radiologists. Science, 1963, **142:** 1492.
19. COURT-BROWN, W. M. AND DOLL, R.: *Leukemia and Aplastic Anaemia in Patients Irradiated for Ankylosing Spondylitis.* (Med. Research Council, Spec. Rep. Series, No. 295) 135 pp. Her Majesty's Stationery Office, London, 1957.
20. STEWART, A., WEBB, J. AND HEWITT, D.: Survey of childhood malignancies. Brit. Med. J., 1958, **I:** 1495.
21. MACMAHON, B.: Prenatal x-ray exposure and childhood cancer. J. Nat. Cancer Inst., 1962, **28:** 1173.
22. ØSTER, J.: *Mongolism. A Clincogenealogical Investigation Comprising 526 Mongols Living in Finland and Neighboring Islands in Denmark.* Danish Science Press, Ltd., Copenhagen, 1953.
23. BENDA, C.: *The Child with Mongolism.* Grune and Stratton, New York, N. Y., 1960.
24. UCHIDA, I. AND CURTIS, E. J.: A possible association between maternal radiation and Mongolism. Lancet, 1961, **II:** 848.
25. LUNN, J. E. A survey of Mongol children in Glasgow. Scot. Med. J., 1959, **4:** 368.
26. CARTER, C. D., EVANS, K. A. AND STEWART, A. M.: Maternal radiation and Down's syndrome. Lancet, 1961, **II:** 1042.

27. Schull, W. J. and Neel, J. V.: Maternal radiation and Mongolism. Lancet, 1962, **I:** 537.

28. Sigler, A. T., Lilienfeld, A. M., Cohen, B. H. and Westlake, J. E.: Parental age in Down's syndrome (Mongolism). J. Pediat., 1965, **67:** 549.

29. Lejeune, J., Gautier, M. and Turpin, R.: Etudes des Chromosomes Somatiques de neuf enfants mongoliens. C. R. Acad. Sci. (Paris), 1959, **248:** 1721.

30. Jacobs, P. A., Baike, A. G., Court-Brown, W. M. and Strong, J. A.: The somatic chromosomes in Mongolism. Lancet, 1959, **I:** 710.

31. Böök, J. A., Fraccaro, M. and Lindstein, J.: Cytogenetical observations in Mongolism. Acta Paediat., (Upps.), 1959, **48:** 453.

32. Ferguson-Smith, M.: Cytogenetics in man. A.M.A. Arch. Intern. Med., 1960, **105:** 627.

33. Penrose, C. S.: Mongolism. Brit. Med. Bull., 1961, **17:** 184.

34. Mavor, J. W.: On the elimination of the X-chromosome from the egg of Drosophila Melanogaster by x-rays. Science, 1921, **54:** 277.

35. Mavor, J. W.: The production of non-disjunction by x-rays. J. Exp. Zool., 1924, **39:** 381.

36. Patterson, J. T., Brewster, W. and Winchester, A. M.: Effects produced by aging and x-raying eggs of Drosophila Melanogaster. J. Hered., 1932, **23:** 325.

37. Russell, L. B. and Saylors, C. L.: *The Relative Sensitivity of Various Germ Cell Stages of the Mouse to Radiation-Induced Non-disjunction, Chromosome Losses and Deficiencies. Repair from Genetic Radiation Damage and Differential Radiosensitivity in Germ Cells.* Proc. of Intl. Symposium held at the University of Leiden, the Netherlands. (Sobels, F. H., edit.) Macmillan & Co., New York, N. Y. 1963, p. 313.

38. Mandl, A. M.: The radiosensitivity of germ cells. Biol. Rev., 1964, **39:** 288.

39. Swanson, C. P.: *Cytology and Cytogenetics.* Prentice-Hall, Englewood Cliffs, N. J., 1957.

40. Lea, D. E.: *Action of Radiations on Living Cells.* 2nd Edit., Cambridge University Press, New York, N. Y., 1956.

41. Hollaender, A.: *Radiation Biology.* Vol. 1: *High Energy Radiation.* McGraw-Hill, New York, N. Y., 1954.

42. Purdom, C. E.: *Genetic Effects of Radiations.* Academic Press, New York, N. Y., 1963.

43. Neel, J. V.: *Changing Perspectives on the Genetic Effects of Radiation.* Charles C Thomas, Springfield, Ill., 1963.

44. Muller, H. G.: *The Nature of the Genetic Effects Produced by Radiation.* (Hollaender, A., edit.) *Radiation Biology,* McGraw-Hill, New York, N. Y., 1954. p. 351.

45. Medical Research Council. *The Hazards to Man of Nuclear and Allied Radiation.* A Second Report to the Medical Research Council. Her Majesty's Stationery Office, London. 1960.

46. *Report of the United Nations Scientific Committee on the Effects of Atomic Radiation.* Supplement No. 17 (A/3838), United Nations, New York, N. Y., 1958.

47. *World Health Organization. Effect of Radiation on Human Heredity.* W.H.O., Geneva, 1957.

48. National Academy of Sciences. National Research Council. The Biological Effects of Atomic Radiation. A Report to the Public, 1960.

49. GLASS, H. B. AND RITTERHOFF, R. K.: Mutagenic effect of a 5-r dose of x-rays in Drosophila Melanogaster. Science, 1961, **133:** 1366.
50. BÖÖK, J. A. AND KJESSLER, B.: Meiosis in the human male. Cytogenetics, 1964, **3:** 143.
51. KELSALL, P.: Non-disjunction and maternal age in D. Melanogaster. Genet. Res., (Camb.) 1963, **4:** 284.
52. OHNO, S., KLINGER, H. P. AND ATKIN, N. B.: Human oögenesis. Cytogenetics, 1962, **1:** 42.
53. RUSSELL, W. L.: X-ray induced mutations in mice. Cold Spring Harbor Symp. Quant. Biol., 1951, **16:** 327.
54. RUSSELL, W. L.: Genetic Effects of Radiation in Mammals. In: Hollaender, A. (edit.) *Radiation Biology*, McGraw-Hill, p. 825, New York, N. Y., 1954.
55. RUSSELL, W. L.: Comparison of x-ray induced mutation rates in Drosophila and mice. Amer. Natur., 1956, **90:** 69.
56. RUSSELL, W. L., RUSSELL, L. B. AND CUPP, M. B.: Dependence of mutation frequency on radiation dose rate in female mice. Proc. Nat. Acad. Sci., Washington, 1959, **45:** 18.
57. RUSSELL, W. L., AND RUSSELL, L. B.: The genetic and phenotypic characteristics of radiation-induced mutations in mice. Radiat. Res. Suppl., 1959, **1:** 296.
58. CHARLES, D. R., TIHEN, J. A., OTIS, E. M. AND GROBMON, A. B.: Genetic effects of chronic x-irradiation exposure in Mice. Genetics, 1961, **46:** 5.
59. WALLACE, B. AND DOBZHANSKY, T.: *Radiation, Genes and Man*. Holt, Rinehart & Winston, New York, N. Y., 1959.
60. LUSH, J. L. AND HAZEL, L. N.: Genetic effect of irradiating swine [from Neel, Ref. 43 above].
61. RUSSELL, W. L.: The Effect of Radiation Dose Rate and Fractionation on Mutation in Mice. In: *Repair from Genetic Radiation Damage and Differential Sensitivity in Germ Cells*. F. H. Sobels (edit.) Macmillan, New York, N. Y., 1963, p. 205.
62. RUSSELL, W. L., RUSSELL, L. B. AND KELLY, E. M.: Radiation dose rate and mutation frequency. Science, 1958, **128:** 1546.
63. MOTTRAM, J. C.: The effect of carbon dioxide on the occurrence of non-disjunction in Drosophila. J. Exp. Biol., 1930, **7:** 370.
64. MICHAELSON, S. M., THOMSON, R. A. E. AND HOWLAND, J. W.: Physiologic aspects of microwave irradiation of mammals. Amer. J. Physiol., 1961, **201:** 351.
65. DEICHMANN, W. B., STEPHENS, F. H., KEPLINGER, M. AND LAMPE, K. F.: Acute effects of microwave radiation on experimental animals. J. Occup. Med., 1959, **1:** 369.
66. LINKE, C. A., TOWNSBERRY, W. AND GOLDSCHMIDT, V.: Effects of microwaves on normal tissues. J. Urol., 1962, **88:** 303.
67. GUNN, S. A., GOULD, T. C. AND ANDERSON, W. A.: The effect of microwave radiation on morphology and function of rat testes. Lab. Invest., 1961, **10:** 301.

Appendix B
Pub. #4

REPRODUCTIVE AND MARITAL EXPERIENCE OF PARENTS OF CHILDREN WITH DOWN'S SYNDROME (MONGOLISM)

ARNOLD T. SIGLER, M.D.
BERNICE H. COHEN,
PH.D., M.P.H., F.A.P.H.A.
ABRAHAM M. LILIENFELD,
M.D., M.P.H., F.A.P.H.A.
JEANNETTE E. WESTLAKE,
R.N., M.P.H.
and
WILLIAM H. HETZNECKER, M.D.
Baltimore, Md.

From the Department of Pediatrics, Harriet Lane Home, Children's Medical and Surgical Center, School of Medicine; and Department of Chronic Diseases, School of Public Health, The Johns Hopkins University

Reprinted from

THE JOURNAL OF PEDIATRICS
St. Louis

Vol. 70, No. 4, Pages 608-614, April, 1967

Reproductive and marital experience of parents of children with Down's syndrome (mongolism)

An epidemiologic study of the parents and siblings of 216 children with Down's syndrome and of 216 control children matched on the basis of maternal age at the time of the child's birth demonstrated no differences in the frequencies of abortions, stillbirths, or congenital abnormalities, nor did the siblings of the children with Down's syndrome have a higher frequency of deaths from acquired causes than did the siblings of the controls. Mothers in the two groups were similar in fertility and there were no differences in their menstrual histories. A significantly higher frequency of multiple marriages prior to the birth of the index child was observed in the mothers of the affected children. Some possible interpretations of these observations are discussed.

Arnold T. Sigler, M.D.,* Bernice H. Cohen, Ph.D., M.P.H., F.A.P.H.A., Abraham M. Lilienfeld, M.D., M.P.H., F.A.P.H.A.,** Jeannette E. Westlake, R.N., M.P.H., and William H. Hetznecker, M.D.**

BALTIMORE, MD.

From the Department of Pediatrics, Harriet Lane Home, Children's Medical and Surgical Center, School of Medicine; and Department of Chronic Diseases, School of Public Health, The Johns Hopkins University.

Supported by United States Public Health Service, Research Branch, Division of Radiological Health, Contract No. SAph 76367, and in part by National Cancer Institute Grant No. CT 5085 and National Heart Institute Grant No. HE5297.

Some of the computations in this paper were done in the Computing Center of the Johns Hopkins Medical Institutions, which is supported by Research Grant FR-00004 from the National Institutes of Health.

**Part of this study was performed while Dr. Sigler was assigned to the Research Branch, Division of Radiological Health, United States Public Health Service. Address, Department of Pediatrics, The Johns Hopkins Hospital, Baltimore, Md. 21205*

***Dr. Lilienfeld is a recipient of a Research Career Award No. K6-GM-13901 and Dr. Cohen is a recipient of a Research Career Development Award No. K3-GM-5590, both from the National Institute of General Medical Sciences.*

Vol. 70, No. 4, pp. 608-614

RECENT cytogenetic observations stimulated an epidemiologic study of the possible relationships between certain factors postulated to cause chromosomal aberrations and the occurrence of clinically diagnosed Down's syndrome. Among the factors studied were parental radiation exposure, reproductive patterns, and marital history. The observations in respect to radiation exposure and parental age have been published in detail.[1,2] Briefly, the mothers of children with Down's syndrome had a history of significantly increased exposure to fluoroscopic and therapeutic radiation prior to the birth of the child with Down's syndrome. No significant difference in the radiation exposure of the fathers was observed. A surprisingly high

frequency of exposure to radar, however, was noted among the fathers of the children with Down's syndrome. Though there was no positive statistical association of paternal age and the birth of a child with Down's syndrome, there was a significant relationship with advanced maternal age.

Many of the earlier studies have examined the reproductive and fertility patterns of parents of children with Down's syndrome.[3-12] This investigation re-examines these characteristics not only in mothers of affected children but also in a comparable series of mothers of control children.

METHOD

A detailed description of the methods used in this investigation is contained in previous reports[1, 2] and this is only briefly reviewed here.

Several Baltimore sources made available the names of 421 children with a diagnosis of mongolism. For the parents to be eligible for interview, the child must have been Caucasian and born in greater Baltimore after Jan. 1, 1946, and before Oct. 1, 1962.

After eliminating those who did not meet these requirements, 288 children with Down's syndrome were available for study. Those eliminated either could not be located in the city directory, were not born in Baltimore, were not Caucasian, or were too old.

Birth certificates of the children with Down's syndrome were located. To ascertain control subjects the birth certificate of each "case" was systematically matched with another birth certificate on the basis of: (1) hospital of birth (or birth at home), (2) sex, (3) date of birth, and (4) maternal age at the time of birth of the child. All "cases" were matched with controls of identical sex, race, and place of birth. In 84.7 per cent of the matched families, the birth dates of the children and ages of their respective mothers were the same. The mean age for the mothers of the children with Down's syndrome was 32.6 years and for the control mothers was 32.5 years.

Each eligible child reported to have Down's syndrome was examined by the senior author (A. T. S.). When the index child was deceased, confirmation of the diagnosis was based on data in medical and hospital records.[2] Of the 288 children, 9 who were deceased or unavailable were eliminated because their medical records did not list the required number of signs to confirm the diagnosis. Another nine were rejected after personal examinations because of negative or equivocal diagnosis. In addition to those 18 rejected on the basis of diagnosis, 54 more were eliminated for the following reasons:

Parents of mongoloid child refused to cooperate	17
Parents of control child refused to cooperate	20
Unable to locate family of mongoloid child	15
Parents of mongoloid child were unable to give adequate interview	2

Thus of the original 288 cases available for study, 72 were eliminated, leaving 216 accepted for study. In every instance in which a family refused to cooperate, the corresponding matched control was also eliminated.

The interviewing of case and of control families was performed by five well-qualified women and in special instances by a physician. The approach to the families with an affected child and to the families of the controls was uniform. The interviewers were not informed as to which family had the abnormal index child; recognition of the family of the child with Down's syndrome was not usually made until the actual interview was conducted. Obstetrical hospital records as well as birth certificates on all pregnancies were checked for miscarriages, stillbirths, and the presence of other congenital abnormalities.

RESULTS

Reproductive history. The lifetime reproductive history of the mothers of the children with Down's syndrome and of the controls is summarized in Table I. There is a striking similarity between the two groups with respect to fertility experience and preg-

nancy wastage. There were no significant differences in the number of pregnancies, abortions, or stillbirths either before or after the birth of the index child. Prior to the birth of the index child, 1.7 per cent of the pregnancies of the mothers of the Down's group and 2.5 per cent of the mothers of the control group ended in stillbirth, whereas 14.2 per cent of the pregnancies of the mothers of the Down's children ended in abortion as compared to 12.2 per cent of the mothers of the controls. Following the birth of the index child, the incidence of stillbirths was 1.1 per cent in each group of mothers, while 14.8 per cent of the mothers of the affected children and 15.4 per cent of the mothers of the controls had abortions. In addition, there were no significant differences for either birth or pregnancy order of the index child. Similarly, there were no important differences in the interval of time between the preceding pregnancy and the birth of the index child, or in the interval of time following the index child's birth and subsequent pregnancies. The number of neonatal deaths and of deaths during later childhood occurring in the siblings of the mongoloid children and controls was also very similar: 95.6 per cent of the siblings of the children with mongolism and 95.2 per cent of those of the controls were still alive at time of interview.

Menstrual history. Slightly fewer mothers of the children with Down's syndrome were still menstruating at the time of interview; the mean age at menopause for the mothers of the affected children was lower than that of the mothers of the controls. However, these differences are not statistically significant (Table II). The two groups also showed no differences with respect to menstrual irregularities, such as a change in duration of menses or in the interval between menses. Furthermore, there was no increase in any type of menstrual irregularity just before the birth of the index child. However, slightly more mothers of children with Down's syndrome reported having to consult a physician at some time during their lives for "menstrual difficulties"—usually menorrhagia.

Marital history. A significantly greater number of multiple marriages before the birth of the index child was recorded for the mothers of the children with Down's syndrome. There were 16.2 per cent of the mothers of affected children who were married two or more times, as compared to only 6.9 per cent of the mothers of the controls ($.01 > p > .001$) (Table III). Of the multiple marriages, 6 in the case group and 5 in the control group remarried because of the death of the previous mate; in addition 28

Table I. Pregnancy wastage in mothers of children with Down's syndrome and in mothers of controls by maternal age and by time relationship to index child

Maternal age groups	*Prior to index child*				*Subsequent to index child*			
	Total pregnancies		*Abortions and stillbirths* (%)*		*Total pregnancies*		*Abortions and stillbirths† (%)*	
	Down's	*Controls*	*Down's*	*Controls*	*Down's*	*Controls*	*Down's*	*Controls*
15-19	1	4	100.0	0	10	16	10.0	0
20-24	32	36	25.0	19.9	52	64	11.5	18.8
25-29	43	57	16.3	17.6	41	47	9.7	23.4
30-34	127	105	15.8	14.3	44	32	20.5	9.4
35-39	185	167	15.7	14.4	28	24	28.6	12.5
40-44	135	148	13.3	13.6	1	5	0	40.0
45-49	4	0	25.0	0	0	0	0	0
50 +	0	0	0	0	0	0	0	0
Total	527	517	15.9	14.7	176	188	15.9	16.5

*For per cent of stillbirths, $p > .30$. For per cent of abortions, $p > .30$.

†For per cent of stillbirths, no difference. For per cent of abortions, $p > .80$.

marriages in the case group ended by annulment or divorce as compared to 9 in the control group. However, as was observed in the total series of mothers, the examination of the reproductive histories of the mothers who were divorced or separated failed to reveal differences in fertility or occurrence of pregnancy wastage.

The difference in marital history of mothers of the children with mongolism and of controls was puzzling. Since mothers of children with mongolism have been shown also to have more radiation than mothers of control children,[1] it seemed worthwhile to determine whether the greater number of multiple marriages for case mothers might be due to some factor related to both radiation exposure and marital dissolution. From Table IV, it is apparent that among those mothers with *no* reported history of radiation, the

Table II. Menstrual history of mothers of children with Down's syndrome and of control children

Data	*Down's* $N = 216$	*Controls* $N = 216$	*P value*
Mean age at menarche (years)	13.56	13.44	.412
Mean age at menopause (years)	45.21	45.93	.276
Still menstruating (%)	70.60	77.60	.101
Operative menopause (%)	39.30	38.30	.907
Always regular period (%)	87.50	87.00	.878
Consulting physician for menstrual difficulty (%)	17.10	10.70	.060
Mean duration of menstrual period (days)	5.72	5.54	.204
Mean interval between periods (days)	28.96	28.90	.741

Table III. Marital and reproductive history of mothers of children with Down's syndrome and of control children

Data	*Down's* $N = 216$	*Controls* $N = 216$	*P value*
Married twice or more before birth of index child (%)	16.2	6.9	< .01
Married once or more following birth of index child (%)	1.4	0.5	> .30
Median number of years married before birth of index child	8.13	8.48	> .30
Median number of years married before first pregnancy ended	1.93	1.99	> .50
Median interval between previous pregnancy and birth of index child	2.93	3.21	> .50

Table IV. Frequency of mutliple marriages and/or alliances according to radiation history of mothers of children with Down's syndrome and of controls

	*All mothers irrespective of radiation history**			*Mothers not irradiated*			*Irradiated mothers†*			*Irradiated mothers fluroscopic and/or therapeutic*		
	Known marital history	*With multiple marriages*		*Known martial history*	*With multiple marriages*		*Known marital history*	*With multiple marriages*		*Known marital history*	*With multiple marriages*	
	(No.)	*(No.)*	*(%)*	*(No.)*	*(No.)*	*(%)*	*(No.)*	*(No.)*	*(%)*	*(No.)*	*(No.)*	*(%)*
Mongols	215	35	16.3	104	15	14.4	104	19	18.3	54	10	18.5
Controls	215	15	7.0	124	7	5.6	83	8	9.6	27	3	11.1

*Total mothers including those with unknown radiation history, but excluding 1 case mother and 1 control mother with unknown marital history.

†Including all types of radiation: diagnostic, therapeutic, and/or fluoroscopic.

mothers of children with Down's syndrome had a significantly higher frequency of multiple marriages than mothers of the control children ($p < .05$). Although there was also a higher frequency of multiple marriages for irradiated mothers of children with mongolism, the difference is not statistically significant ($.10 > p > .05$). When only fluoroscopic and therapeutic irradiation were considered, the trends were similar but the differences were still not significant ($p > .30$). Thus the higher frequency of multiple marriages prior to birth of the index child among case mothers as compared to control mothers cannot be attributed to an association with radiation, but rather appears to represent an independent relationship.

Religion and education. A larger proportion of both Catholic and Jewish parents were found in the group of children with mongolism, but the differences from the parents of the controls are not statistically significant (Table V). Of the parents of the children with Down's syndrome, 24.5 per cent were of differing religions, as compared to 19.2 per cent of the parents of the controls. In the case group, 13.9 per cent of the marriages involved a Catholic mother and a father of some other religion, as compared to 9.7 per cent of the controls. Conversely, 5.6 per cent of the marriages of parents in the case series involved a Catholic father and a mother of another religious preference, while this same combination applied to 6.9 per cent of the parents of the controls.

In view of the higher frequency of multiple marriages among mothers of the cases, we thought it would be of interest to determine the religious distribution of those mothers who had multiple marriages. Of such mothers, 38 per cent of the case mothers were Catholic and 12 per cent Jewish, as compared to 33 per cent and 0 per cent for the control mothers; these differences were not statistically significant.

Similar educational backgrounds were reported by each group of parents: 77.8 per cent of the mothers of the affected children and 76.9 per cent of the mothers of the controls had no education following high school, while 67.1 per cent and 72.2 per cent of the case and control fathers, respectively, had no post-high school education.

Table V. Religious preferences of parents of children with Down's syndrome and of control children

	*Mothers**		*Fathers†*	
Religion	*Down's, N = 214 (%)*	*Controls, N = 215 (%)*	*N = 212 N = 206 (%)*	*Controls, N = 212 (%)*
Catholic	50.9	43.3	44.7	41.0
Jewish	8.4	6.5	8.7	5.7
Protestant	38.8	48.8	44.7	50.9
Other	1.9	1.4	1.9	2.4

*$\chi^2 = 4.50$; $p > .20$.
†$\chi^2 = 2.64$; $p > .30$.

DISCUSSION

With the use of controls matched for maternal age at the time of birth of the index child, date of birth, sex, and hospital of birth of the index child, this study demonstrated that the reproductive, menstrual, and religious experience of mothers of children with Down's syndrome was not different from that of mothers of controls.

Of particular interest is the significantly greater number of multiple marriages due to separation and divorce prior to the birth of the index child found in the mothers of the Down's children as compared to mothers of controls. Although broken marriages might be expected *following* the birth of a defective child, they are not as easily explained *before* the birth. This increase in multiple marriages is noteworthy since the frequency of Jews and Catholics, known for their low divorce rates, is relatively higher in the Down's group, although this difference is not statistically significant. The etiologic basis of a relationship between multiple marriages and the occurrence of Down's syndrome in offspring is not clear. It is quite possible that in examining a great number of factors, one or more "chance" associations may appear. Whether this multiple marriage association is

a "chance" finding or a real one, therefore, remains to be determined.

Pregnancy wastage, fertility, and menstrual irregularities have been the subject of frequent comment in studies of Down's syndrome. Unfortunately, most comparisons dealing with reproductive history have been made either with unsuitable controls or with no controls at all. Benda[3] found his group of mothers of children with mongolism to have an abortion frequency of 31.2 per cent and compared this figure to that of 10.6 per cent for the general population. Other authors, including Murphy,[4] Beidleman,[5] and Engler[6] also reported that mothers of children with Down's syndrome have an abnormally high abortion rate. Down,[7] Beidleman,[5] Benda,[3] and Engler[6] also indicated that the pregnancy-free interval prior to the birth of the affected child was longer than normal. Each of these studies, however, failed to take into account the importance of controlling maternal age when dealing with age-related reproductive factors. Smith and Record[8] also reported higher abortion rates for mothers of children with mongolism than for controls and made an attempt to control for maternal age, but the scarcity of older control mothers led to the selection of a smaller and younger control group.

Similarly, Coppen and Cowie[9] in 1960 observed that of 93 pregnancies in 55 Down's mothers, 31 per cent ended in abortion or stillbirth. However, Ingalls, Babbott, and Philbrook[10] found a 15.5 per cent abortion rate in mothers of cases versus 9.4 per cent in the controls. In contrast, Øster[11] reported that 9.7 per cent of 1,523 pregnancies of Down's mothers ended in stillbirth or abortion, and more recently Lunn[12] found no difference in fertility and no higher rate of abortions in Down's mothers when compared to age matched controls in Glasgow.

Since the increased frequency of abortions is at least in part related to advancing maternal age,[13] and since the frequency varies in different populations and with different modes of data collection, the importance of an adequate comparison group controlled by maternal age cannot be overemphasized. The finding in this study that mothers of children with mongolism show no higher frequency of abortions, stillbirths, or other offspring with congenital abnormalities, suggests that meiotic nondisjunction occurs in relatively few viable ova in any one female during a lifetime.

SUMMARY

An epidemiologic study of the families of 216 children with Down's syndrome and 216 control children matched on the basis of maternal age at the time of the child's birth demonstrated no difference in abortions, stillbirths, congenital abnormalities, or increased sibling deaths from acquired causes in the case group as compared with the control group. Fertility in the mothers of affected children, both before and after the birth of the child, was similar to that of the controls. No significant difference in maternal menstrual history was found. These data suggest that in families containing a child with Down's syndrome, except where the mother is young at the time of birth of the affected child, the risk of having a subsequent pregnancy end in abortion, stillbirth, another child with mongolism, or any other congenital abnormality is largely related to the risk associated with the maternal age at that time, rather than with the Down's syndrome itself.

The significantly higher incidence of multiple marriages prior to the birth of the index child observed in mothers of Down's children as compared to control mothers is noteworthy and requires further study.

We wish to acknowledge the contributions of Mrs. Susan Baker who was responsible for the computer programming, and of Drs. Robert Cooke, Barton Childs, and Simon Abrahams, and Mrs. Charlotte Benesch for their helpful suggestions. In addition, generous cooperation and support were given by Mr. Sidney Norton of the Department of Vital Statistics, by the Baltimore Society for Retarded Children, the principals of the many schools for the retarded, and the administrators and medical records personnel of the Baltimore hospitals.

REFERENCES

1. Sigler, A. T., Lilienfeld, A. M., Cohen, B. H., and Westlake, J. E.: Radiation exposure in parents of children with mongolism (Down's syndrome), Bull. Johns Hopkins Hosp. **117:** 374, 1965.
2. Sigler, A. T., Lilienfeld, A. M., Cohen, B. H., and Westlake, J. E.: Parental age in Down's syndrome (mongolism), J. PEDIAT. **67:** 631, 1965.
3. Benda, C. E.: The child with mongolism, New York, 1960, Grune & Stratton, Inc.
4. Murphy, M.: The birth order of Mongol and other feebleminded children, Human Biol. **8:** 256, 1936.
5. Beidleman, B.: Mongolism: a selective review, Am. J. Ment. Deficiency **50:** 35, 1945.
6. Engler, M.: Mongolism (peristatic amentia), Baltimore, 1949, The Williams & Wilkins Company.
7. Down, J. L.: Discussion of Shuttleworth, G. E.: Mongolian imbecility, Brit. M. J. **2:** 661, 1909.
8. Smith, A., and Record, R. G.: Fertility and reproductive history of mothers of mongol defectives, Brit. J. Prev. & Social Med. **9:** 89, 1955.
9. Coppen, A., and Cowie, V.: Maternal health and mongolism, Brit. Med. J. **1:** 1843, 1960.
10. Ingalls, T. H., Babbott, J., and Philbrook, R.: The mothers of Mongoloid babies: A retrospective appraisal of their health during pregnancy, Am. J. Obst. & Gynec. **74:** 572, 1957.
11. Øster, J.: Mongolism: A clinicogenealogical investigation comprising 526 Mongols living in Seeland and neighboring islands in Denmark, Copenhagen, 1953, Danish Science Press.
12. Lunn, J. E.: A survey of Mongol children in Glasgow, Scottish M. J. **4:** 368, 1959.
13. Warburton, D., and Fraser, C. F.: Spontaneous abortion risks in man: Data from reproductive histories collected in a medical genetics unit, Am. J. Human Genet. **16:** 1, 1964.

Appendix B
Pub. #5

THE EPIDEMIOLOGICAL STUDY OF MONGOLISM IN BALTIMORE

Bernice H. Cohen, Ph.D., M.P.H.,† and
Abraham M. Lilienfeld, M.D., M.P.H.‡

Reprinted from
ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Volume 171, Article 2, Pages 320–327
September 24, 1970

THE EPIDEMIOLOGICAL STUDY OF MONGOLISM IN BALTIMORE *

Bernice H. Cohen, Ph.D., M.P.H.,† and
Abraham M. Lilienfeld, M.D., M.P.H.‡

Department of Chronic Diseases
The Johns Hopkins University School of Hygiene and Public Health
Baltimore, Md.

The epidemiological study of mongolism in Baltimore was initiated primarily to determine whether there was a relationship between parental exposure to ionizing radiation and the occurrence of mongolism among offspring. The principal stimuli for this inquiry were the known relationship between ionizing radiation and chromosomal aberrations, the association of leukemia and mongolism, and the leukemogenic effect of radiation. In addition to collecting data for this major objective, information was obtained and analyzed concerning other factors, such as parental age and maternal reproductive patterns, which might be associated with chromosomal aberrations. In this report, we shall summarize the study results [1-3] and briefly describe the procedures of a supplementary investigation undertaken this year and currently in progress.

METHOD

A detailed description of the methods used in the original study has already been reported and will, therefore, be reviewed only briefly here. The names of 421 children with a diagnosis of mongolism were made available from several Baltimore sources. To be eligible for inclusion in the study, the child had to be Caucasian and born in the greater Baltimore area between January 1, 1946, and September 30, 1962. Those who did not meet these requirements were eliminated from the study (51 not born in Baltimore, 38 not Caucasian, 17 too old, 17 whose families could not be located in the city directories, and 8 whose birth certificates could not be located). This left 288 with an initial diagnosis of mongolism. The birth certificates of all the 288 eligible children were then obtained. To select control subjects, the birth certificate of each case was sys-

* The original studies were supported in part by the United States Public Health Service, Research Branch, Division of Radiological Health Contract No. SAph 76367, and in part by National Cancer Institute Contract No. CT 5085 and National Heart Institute Contract No. HE 5297. The current studies are being supported jointly by the Advanced Research Project Agency of the Department of Defense under Contract No. DA DA 17-69-C-9154, and by the Environmental Control Administration, Consumer Protection and Environmental Health Service, Public Health Service, Department of Health, Education and Welfare, Contract No. CPE-R-69-24.

† Recipient of Research Career Development Award No. K3-GM-5590 from the National Institute of General Medical Sciences.

‡ Recipient of Research Career Award No. K6-GM-13,901 from the National Institute of General Medical Sciences.

tematically matched with another birth certificate on the basis of: (1) hospital of birth, or birth at home, (2) sex, (3) maternal age at the time of birth of the child, and (4) date of birth.

Each eligible child reported to have mongolism was examined by a pediatrician. A set of physical criteria for mongolism was used to determine whether the child should be accepted as a case. Those who did not meet these criteria were eliminated from the study. Of the 288 cases, 18 were excluded because of the absence of diagnostic criteria, and 54 cases were eliminated because of refusal to cooperate, inability to locate the family, or inability to obtain an adequate interview. Consequently, 216 cases were available for the final analysis.

The interviewing of the case and control families was performed by five well-qualified women. Interviewers were not informed which were cases and which were controls; recognition of the family with Down's syndrome did not usually occur until the actual interview was conducted. Questions about radiation exposure were always phrased without reference to the birth of the index child. In addition, medical records—including obstetrical records—were reviewed with regard to reproductive histories and radiation exposure independently of the interview.

Results

Radiation Exposure

A summary of the histories of radiation exposure of the mothers of the cases and controls is presented in Table 1. For mothers with definite "yes" or "no" answers for radiation exposure, 50% of the mothers of mongols reported no radiation as compared to 59.9% of the control mothers—a difference which is statistically significant ($P < .05$). It is clear from this Table that the increased exposure history of mothers of the mongols is mainly a result of fluoroscopic and therapeutic radiation or of combinations of multiple sources of radiation. In contrast to the mothers, the fathers of the mongols did not have significantly greater exposure to radiation than did the control fathers (Table 2). Although a somewhat smaller proportion of fathers of mongols reported no radiation, and a slightly larger proportion had diagnostic radiation as compared to fathers of controls, none of these differences was statistically significant, and there were no differences in the categories in which therapeutic and/or fluoroscopic radiation were included.

In an attempt to determine whether there were any additional differences in exposure to radiation or other energy sources, occupational histories were reviewed: 7.9% of the mothers of mongols, but only 3.3% of the control mothers, had worked in a professional or technical capacity in medical fields ($P < .05$). Eight mongol mothers, in contrast to three control mothers, gave histories of definite x-ray and/or fluoroscopic exposures in all types of occupations, prior to the conception of the index child.

No differences were found in the occupations of the fathers of the mongols and the controls, except for a higher frequency of military service for the fathers of mongol children—63.1%, as compared with 56.6% for control fathers. In addition, a history of radar exposure was obtained from the fathers, which indicated that 8.7% of the fathers of the children with mongolism and 3.3% of

TABLE 1

SUMMARY OF MATERNAL RADIATION EXPOSURE PRIOR TO BIRTH OF INDEX CHILD

Type of Radiation	Mothers of Mongols (%)	Mothers of Controls (%)
No radiation	50.0	59.9
Radiation		
Diagnostic only	24.0	27.1
Fluoroscopic only	4.8	3.4
Therapeutic only	3.3	1.4
Diagnostic and fluoroscopic	6.7	3.9
Diagnostic and therapeutic	3.4	2.9
Fluoroscopic and therapeutic	1.0	0.5
Diagnostic, fluoroscopic, and therapeutic	6.3	0.9
Unknown	3.7	4.2

the control fathers had had contact with radar, both in and outside of the armed forces—a difference which is of borderline statistical significance ($P < .02$).

Two measures of the degree of relationship between maternal radiation exposures and mongolism were computed from the data. TABLE 3 shows that the estimated relative risk is 1.5, that is, mothers exposed to radiation had a 50% greater chance of having an offspring afflicted with Down's syndrome. From this relative risk, it was also possible to determine the attributable risk, that is, the estimated proportion of mongols in the population associated with maternal radiation exposure, using the method proposed by Levin;[4] this was computed to be 17%. It should be understood that this percentage reflects not only the relative risk but also the frequency of radiation exposure in the general population and will, therefore, differ in various population groups.

TABLE 2

SUMMARY OF PATERNAL RADIATION EXPOSURE PRIOR TO BIRTH OF INDEX CHILD

Type of Radiation	Fathers of Mongols (%)	Fathers of Controls (%)
No radiation	43.7	50.0
Radiation		
Diagnostic only	31.5	25.5
Fluoroscopic only	5.6	5.4
Therapeutic only	2.0	1.9
Diagnostic and fluoroscopic	8.6	10.3
Diagnostic and therapeutic	5.6	4.9
Fluoroscopic and therapeutic	1.0	1.0
Diagnostic, fluoroscopic, and therapeutic	2.0	1.0
Unknown	8.8	5.6

Reproductive and Menstrual History

An analysis of the lifetime reproductive histories showed striking similarities in menstrual history, fertility experience, and pregnancy wastage in mothers of both the cases and controls.[3] No significant differences were noted in the number of pregnancies, abortions, or stillbirths, before or after the birth of the index child. No statistically significant differences were observed with regard to the pregnancy order or birth order of the index child, interval of time between the preceding pregnancy and birth of the index child, or from the latter to subsequent births. Moreover, the frequency of neonatal deaths and childhood deaths among siblings of the mongoloid children was similar to those among the controls.

TABLE 3

COMPUTATION OF RELATIVE RISKS FOR MATERNAL RADIATION EXPOSURE *

Maternal Radiation History	Mothers of Mongols	Mothers of Controls
No radiation	104	124
Radiation	104	83
	208	207

* Estimated relative risk $= \dfrac{124 \times 104}{83 \times 104} = 1.5$

Marital History

A significantly greater number of multiple marriages before the birth of the index child was recorded for the mothers of the mongols. There were 16.2% of mothers of affected children who were married two or more times, as compared to only 6.9% of mothers of controls. Of the multiple marriages, 6 in the case group and 5 in the control group had remarried because of the death of the previous spouse; however, 28 marriages in the case group had ended in annulment or divorce as compared to only 9 in the control group.

Because of the higher frequency of radiataion exposure among mothers of mongols, it was considered desirable to determine whether multiple marriages were also associated with radiation exposure. Perhaps, the higher frequency of multiple marriages among mothers of mongols is merely a reflection of a higher frequency of radiation exposure among those who have had multiple marriages. However, an analysis indicated that these two were independently related to mongolism (TABLE 4). Among mothers who had not been irradiated, 14.4% of mothers of mongols but only 5.6% of control mothers had multiple marriages ($P < .05$).

Other Factors

The cases and controls were compared with regard to several other variables, including residential history,[2] religion,[3] and educational background.[3] No statistically significant differences between the two groups were observed in these factors.

Maternal and Paternal Ages

The relationship of mongolism to maternal age has been well substantiated, and did not require any additional confirmation in this study. In fact, the controls were matched to the mongol children by maternal age, thereby eliminating the possibility of analyzing these pairs for a maternal age effect.

We were, however, interested in the possibility of a paternal age effect, since

Table 4

Frequency of Multiple Marriages among Study Mothers with Known Marital and Radiation Histories

	Mothers of			
	Mongols		Controls	
Radiation History	Total	Multiple Marriages (%)	Total	Multiple Marriages (%)
No reported history of radiation	104	14.4	124	5.6
Reported history of radiation	104	18.3	83	9.6
Reported history of fluoroscopic and/or therapeutic radiation	54	18.5	27	11.1

there was a suggestion from some recent studies that such an effect might exist, and we were also not satisfied that earlier studies had completely excluded such a possibility.[5-7] The difficulty in analyzing data for a paternal age effect stems from the high correlation of paternal with maternal ages. The approach in the present study, however, permitted the examination of the effects of maternal and paternal ages independently, in a separate analysis.

In this study, the matching of the birth certificate of each mongol with that of a subsequent birth with respect to maternal age, permitted us to determine whether there were differences with respect to paternal age distributions. Then a different series of controls was obtained by selecting another set of birth certificates matched to the certificates of the mongol cases with respect to paternal age to determine whether there were differences in maternal age distributions.

The results of this analysis clearly indicated the presence of a maternal age effect but no paternal age effect. Table 5 shows the maternal age effect with paternal age controlled. Note that in every paternal age group except the youngest, the mothers of the mongols were older than those of the controls, the

TABLE 5

MATCHED PAIR ANALYSIS OF MATERNAL AGE WITH PATERNAL AGE CONTROLLED (PAIRED t TEST)

Paternal Age Group	No. of Mothers	Mean Differences *	t	P
20–24	22	−0.09	0.14	NS
25–29	40	+0.73	1.03	NS
30–34	41	+3.4	3.09	<.01
35–39	53	+2.3	6.28	<.001
40–44	39	+4.9	6.20	<.001
45+	20	+0.8	0.53	NS
All cases	215	2.3	6.05	<.001

* Mongol maternal age minus control maternal age.

mean differences attaining statistical significance in the older age groups, 30–45 years. The group over 45 years of age is not significant, probably because of its small size, although the difference is in the same direction. When all age groups are pooled, the maternal age difference is statistically significant at the .001 level.

On the other hand, as shown in TABLE 6, when paternal age was examined with maternal age controlled, there were no significant differences, except for one maternal age group (30–34 years) in which the fathers of mongols were younger than the fathers of controls. Thus, no consistent age pattern is discernible in the fathers. Naturally, in such a study, the number of cases imposes limitations with regard to the detection of a small effect. It would appear, however, that the absence of a significant finding with regard to paternal age probably eliminates at least a moderate effect of paternal age. The detection of a smaller paternal age effect would require a larger series of cases.

TABLE 6

MATCHED PAIR ANALYSIS OF PATERNAL AGE WITH MATERNAL AGE CONTROLLED (PAIRED t TEST)

Maternal Age Group	No. of Fathers	Mean Difference *	t	P
15–19	6	0	0	NS
20–24	34	0	0	NS
25–29	30	−0.07	0.07	NS
30–34	46	−3.07	3.79	<.001
35–39	62	+0.45	0.66	NS
40+	37	+1.1	1.05	NS
All cases	215	−0.34	0.79	NS

* Mongol paternal age minus control paternal age.

Discussion

The results of this study indicate that the mothers of mongol children received significantly more radiation, particularly fluoroscopy and therapeutic radiation, than the mothers of control children. In fact, for combined radiation from one or more diagnostic, fluoroscopic and therapeutic sources, the frequency of mothers of mongol children that had such procedures was seven times that of control mothers. Of additional interest was the observation that significantly more mothers of mongols were employed in professional or technical occupations in the medical field. The consistency of these relationships is notable.

The only other two associations that appeared in the analysis were the well-documented association of mongolism with maternal age, and the higher frequency of multiple marriages among the mothers of the mongol children as compared to the controls. Although broken marriages might be expected following the birth of a defective child, they are not as easily explained when they occur before the birth. It is quite possible, however, that in a study in which a great many factors are examined, one or more chance associations will appear. Whether this multiple marriage association is a chance finding remains to be determined. With respect to pregnancy wastage, fertility, and menstrual irregularities, the mothers of the mongol children did not differ from the control mothers nor did they show a higher frequency of other offspring with congenital abnormalities.

The radiation history of the fathers provided a contrast to that of the mothers. There was a marked similarity in the history of radiation exposure reported by the fathers of mongols and of the controls, except for the suggested relationship between mongolism and paternal radar exposure. Although, with the small numbers available, it is possible that this finding may be a chance observation, it clearly appears worthy of additional investigation, especially since recent studies have also indicated that a small amount of ionizing radiation may be involved in high voltage radar equipment.

In view of the need to confirm the positive findings, the original study was extended, beginning in June 1969, to include additional mongol children born from October 1962 through December 1968. We estimate that it will be possible to obtain an additional 140 cases. The procedures for control selection and interviewing in the current study are essentially the same. However, two features are being added: a validation of military service history and a chromosome study.

All of the names of the fathers of the cases and controls will be checked against armed forces records to determine whether they, in fact, had been in military service and the branch of service. Moreover, information will be obtained on the MOS (Military Occupation Specialty) classification of fathers and, insofar as is discernible from records, whether they worked with radar or at a radar installation.

The chromosome studies are being carried out on all fathers who reported a history of radar exposure in the original series as well as on those reporting such exposure in the current series, in order to determine whether any aberrations (such as aneuploidy, translocations, dicentrics or other aberrations or evidence of breaks) are observed. For a comparison group, the chromosomes of unexposed fathers of the children matched to the exposed fathers are also being studied. As a result of these additions, both series together will probably yield

60–70 radar-exposed fathers, so that a total of approximately 120 chromosome analyses will be performed.

Thus, the investigation in progress not only will serve as an independent replication of the earlier study but will also allow validation of the military service histories as well as explore possible chromosomal changes. Hopefully, the current phase will be completed by the end of 1970.

Summary

An epidemiological study encompassing a population of parents of mongols and matched control children born in Baltimore, Maryland 1946–1962 confirmed the well-documented association of mongolism with older mothers and indicated that the mothers of mongols had been exposed to significantly more radiation, particularly fluoroscopy and therapeutic radiation, than the mothers of control children. Another association, the higher frequency of multiple marriages among the mothers of the mongol children, as compared to the controls (independent of the radiation association), is difficult to interpret and may be a chance finding.

Although there were striking similarities in the diagnostic and therapeutic radiation histories of fathers of mongols and controls, there was a suggested relationship of mongolism with paternal radar exposure.

In order to confirm the findings, an extension of the investigation to include mongols born October 1962 through December 1968 was initiated last June. The current study is an independent replication of the previous study with two added features: (1) a validation of military service and radar exposure, and (2) a chromosome study of radar-exposed fathers and unexposed fathers of matched controls.

References

1. Sigler, A. T., A. M. Lilienfeld, B. H. Cohen & J. E. Westlake. 1965. Parental age in Down's syndrome (mongolism). J. Pediat. **67:** 631.
2. Sigler, A. T., A. M. Lilienfeld, B. H. Cohen & J. E. Westlake. 1965. Radiation exposure in parents of children with mongolism (Down's syndrome). Bull. Johns Hopkins Hosp. **117:** 374.
3. Sigler, A. T., A. M. Lilienfeld, B. H. Cohen, J. E. Westlake & W. H. Hetznecker. 1967. Reproductive and marital experience of parents of children with Down's syndrome (mongolism). J. Pediat. **70:** 608.
4. Levin, M. L. 1953. The occurrence of lung cancer in man. Acta Int. Un. Contra Cancrum **9:** 531.
5. Penrose, L. S. & G. F. Smith. 1966. Down's Anomaly. Little, Brown & Co. Boston, Mass.
6. Mantel, N. & C. R. Stark. 1966–67. Paternal age in Down's syndrome. Amer. J. Ment. Defic. **71:** 1025.
7. Lilienfeld, A. M. & C. H. Benesch. 1969. Epidemiology of Mongolism. The Johns Hopkins Press. Baltimore, Md.

APPENDIX C

APPENDIX C-1	CRITERIA FOR CLASSIFICATION AS DOWN'S CASES
APPENDIX C-2	CRITERIA FOR RADAR EXPOSURE CLASSIFICATION
APPENDIX C-3	MOS AND JOB TITLE CLASSIFICATION FROM ARMY AND NAVY CONSULTANTS
APPENDIX C-4	NAS SEARCH FORM FOR VALIDATION OF MILITARY SERVICE RECORD

APPENDIX C-1

CRITERIA FOR CLASSIFICATION AS DOWN'S CASES

APPENDIX C-1

DOWN'S SYNDROME CRITERIA

Requirements for inclusion in Current Series as a Case of Down's syndrome (Mongolism)

Down's Syndrome Cases - 5 stigmata or more from hospital or physician's records. These are listed on the hospital abstract check list and coded on Card 9 - Col. 19 thru 36.

Exceptions:

If deceased - 3 stigmata plus mention of Mongolism (Down's, etc.) on death certificate or on hospital record or confirmed by physician.

If alive - less than 5 stigmata with chromosome studies done and Trisomy 21 confirmed.

LIST OF STIGMATA FOR ELIGIBILITY AS A DOWN'S SYNDROME CASE

Brachycephaly
Slanted palpebral fissures
Epicanthic folds
Palmar simian lines
Malformed ears
Broad and/or short neck
Web neck
Malformed fingers and/or hands
Nasal abnormality
Hypertelorism
Abnormal palate
Abnormal or furrowed tongue
Abnormal footprints/handprints
Brushfield spots
Abnormal hip angles
Broad and/or short trunk
Congenital heart condition

Index Cases with Fewer than Five Stigmata

2 stigmata

14450 - Trisomy 21 (Dr.) - Heart Condition.

4 stigmata

35320 - Moore Clinic - chromosome study and dermatoglyphics, palmar simian lines, brushfield spots.

15460 - Slanted palpebral fissures, epicanthic folds, palmar simian lines, abnormal palate.

Deceased Mongols

3 stigmata

14010 - Palmar simian lines, abnormal tongue, congenital heart disease.

35010 - Epithantic folds, brushfield spots, heart condition.

35040 - Brachycephaly, slanted palpebral fissures, malformed ears.

35510 - Palmar simian lines, abnormal hip angles, heart condition.

35530 - Epicanthic folds, cleft palate, heart condition.

4 stigmata

35190 - Slanted palpebral fissures, palmar simian lines, malformed thumbs, heart condition.

35230 - Slanted palpebral fissures, malformed hands, nasal abnormality, abnormal tongue.

35520 - Slanted eyes, malformed finger, protruding tongue, heart disease.

APPENDIX C-2

CRITERIA FOR RADAR EXPOSURE CLASSIFICATION

APPENDIX C2

RADAR EXPOSURE CRITERIA

Interview Exposure Classification

Classification as exposed or definitely exposed was assigned for any father who indicated on interview that he definitely worked with or near radar in military service or industry.

Classification as questionable exposure or probably some exposure was assigned for any father who indicated that he had some more remote connection with radar, e.g., mobile radar was used in his unit in military service, radar was used on his ship, he was stationed at a radar park, he worked in industry where radar was used or manufactured but did not work directly with it. "Questionable" here does not refer to doubtful but rather to probably some exposure or a greater likelihood than the general population of having some exposure.

NAS Exposure Classification

Classification of fathers as to exposure in military services was determined by military consultants from the Army and Navy who screened MOS numbers and job descriptions and assessed these as to risk of microwave exposure.

On Army, Air Force, and National Guard lists, those job classifications considered as involving exposure were so indicated by a designation symbol, in some cases with added explanatory material. See attached.

On Navy, Coast Guard, and Marine Corps lists, jobs were evaluated for risk as follows:

No or none,

Maybe low,

Low,

Moderate,

High, and

"?"

Classification as "maybe low," "low," "moderate," and "high" were considered exposed in this study.

Combination of Interview and NAS Exposure Classification

In combining exposure status as determined from interview information and from NAS information, the following summary classifications were established:

(1) None, being no on both records

(2) Probably none, being no on either interview or NAS and unknown on the other

(3) Questionable or probably low exposure if any, being questionable or probably some exposure on either interview or NAS

(4) Probable exposure, being yes at risk on either interview or NAS but not verified by both

(5) Definite exposure, being definite on both records

(6) High exposure (definite) by both interview and NAS (e.g., high on NAS, definite on interview

Chromosome Study Classification

Fathers included in this study and considered at risk to microwave exposure were classified as "exposed" and "near exposed." Exposed fathers included those who were found to be exposed or definitely exposed on interview or on lists of MOS numbers or job descriptions evaluated by the military service officers or both. Near exposed fathers included those whose exposure was determined to be "questionable" or "probably some exposure on interview."

APPENDIX C-3

MOS AND JOB TITLE CLASSIFICATION FROM ARMY AND NAVY CONSULTANTS

Army

ARMY

MOS #	Job Title	Years
006.00	Basic Training	1955, 1957-61
013	Automotive Mechanic	1946
014	Automobile Mechanic	1941-46
050	Carpenter, Construction	1942-43
051.10	Intermed. Speech Radio Opr.	1955
052	Chief Clerk	1944
052.10	Svc. Sch. - Radio Opr.	1954
055	Clerk - general	1942-45
056	Mail Clerk	1943-44
060	Cook	1943, 1945-47
081	Engineman, Operating	1944
097	Instructor - Repair T&T Central Office Tech.	1942, 1945
. . ///	Rifleman (U.S. Reserves)	1955
111.00	Rifleman Light Weapons Infantryman	1954, 1959
111.10	Automatic Rifleman	1956-7, 1960-62
112.00	Heavy Weapons Infantryman	1955
112.10	Advanced Indiv. Tng; Gunner	1959
112.70	Squad Leader	1956
114	Machinist; Artillery Mechanic	1942
120.00	Advanced Indiv. Tng.	1960
121.00	Combat Const. Specialist	1960
128	Duplicating Machine Opr.	1943
137	Projectionist Motion Picture	1944
140.00	Cannoneér	1961
161	Anti-aircraft cannoneer	1955
162	Anti-aircraft artillery gun crewman	1955

Army

MOS #	Job Title	Years
52.1	Adv. Indiv. Tng.	1955
164	Plumber	1944
164.10	Heavy truck driver	1959
166	Powerman	1944, 1951
170	Technical Aide	1947
174	Radio Repairman	1944
187	Repeaterman, Telephone	1944
188	Ammo Sec., Warehouseman; Duty Soldier, II	1947, 1949-50
191	Rodman & Chainman, Surveying	1947
194	Salvageman	1943
201	Sheet Metal Worker	1943, 1945
228	Surveyor & Instrument Opr.	1940
230	Topo. Surveyor	1946
32	Installer T&T; Switchboard Inst.	1941, 1944
237	Teletypewriter Opr.	1942, 1944, 1947
238	Lineman - T&T	1942-44
239	Teletype Mechanic	1947
242	Tool Room Keeper	1944-45
245	Truck Driver, Heavy	1943-46
252	Foreman Warehouse	1943
268	Accountant	1944
275	Class. Specialist	1944
283	Athletic Instructor	1943
301	Investigator	1946
303	Hospital Orderly	1943
309	Switchboard Opr.	1943
311.10	TC (USAR-Rdy) Radio Mech.	1960

MOS #	Job Title	Years
322	Refrigerator Mechanic	1946
324	Stock Clerk	1943
331.10	Svc. Sch. Man. Cen. O. Rep.	1957
344	Chauffeur	1942
345	Automotive Equip. Opr.; Driver, Ambulance and Truck; Natl. Grd.	1941-46; 1948
348	Auto Parts Clerk	1943, 1946
355	File Clerk	1943
368	Personnel Clerk	1943
383	Fire Fighter	1943
400	Tabulating Machine Opr.	1942
405	Clerk Typist	1943, 1945, 1946, 1949
409	Medical Technician	1943-45
410	Dispatcher, Motor	1944
432	Bandsman, Clarinet	1943
439	Bandsman, Saxaphone	1943
443.10	Marine Div. Machinist	1954
467	Air Compressor Opr.	1944
501	Clerk	1943
502	Admin. NCO; Ch. Clrk; Asst. Foreman Processing;	1943, 1945-46
504	Ammunition Bearer	1943
505	Ammunition NCO	1947
510.00	Construction Hlpr.; Adv. Indiv. Tng; Info. Cen. Opr.	1953-54
511	Small Arms Repairman; Armorer	1943-44
513.10	Mason	1958
515	Filtering	1943

Army

MOS #	Job Title	Years
521	Basic Tng., Non-Specialist	1943-46, 1948-49
522	Duty Soldier; Guard	1943-45
526	Crewman	1943
529	Wrecker Driver	1944
531	Cannoneer	1943-44
539	Chief of Station; Asst. Sec.Ch.	1943-44
540.00	Cannoneer	1955
542	Communications Tech., Basic [illegible], Radio Opr.	1943, 1949
555	Airplane Sheet Metal Wrker.	1944
560.00	TC USAR Rdy Radio Mech.	1959
562.60	TC (USAR-Rdy) Coxswain	1962
566	Duty NCO; Basic Tng.	1943-44, 1946
573	P-Aircraft Welder	1945
580	Remote Control Turret Mach.Gnr.	1944
590	Basic; Laborer; Day Rm. Ordrly, Duty Soldier	1942, 1944-46
60[illegible]	Asst. Gunner; AW Crewman	1944, 1946
603	Gunner	1943
604	Light Machine Gun Crewman	1945
605	Heavy Machine Gunner (P)	1945
606	Anti-aircraft Machingun Crwman.	1944
607	Mortar NCO - Light Mortar	1944-45
609	Leather & Canvas Worker	1946
610	Anti-Tank Gun Crewman; Gnr.Tnk.	1943-45
611	Aerial Gunner	1943, 1946
612	Airplane Armorer/Gunner	1946
614	Lineman	1943
620	Parachute Rigger & Rprmn.	1944

Army

MOS #	Job Title	Years
622	Finance Technical Clk.	1944-45
629	Student; Student Officer	1943-44, 1946
631.10	Wheel Vehicle Mechanic	1961
634	Fuel & Elec. Sys. Rprman.	1955
638	Installer, Repair	1942
640.00	Lt. Vehicle Driver	1954
641	Field Lineman	1942-43
648	Radio Repair	1943
650	Switchboard Opr.	1943-44
651	Platoon Sgt.	1943
652	Sec. Sgt., Sec. Ldr.-Gun	1942-43
653	Squad Ldr.	1944
655	Duty NCO	1944
657	Litter Bearer; Med. Aidman	1944-45
659	Special Svc. Sch. Instructor	1946
667	Message Cen. Clerk	1944-45
670	Master Gunner	1943
673	Medical NCO	1946
675	Messenger	1942, 1944
677	Military Police; Provost Sgt.	1937, 1943-44, 1946
683	Bombsight Mechanic	1945
684	Op. Pow. Plt. Mech.	1944
695	Orderly & Driver	1943
710.00	Clerk; Adv. Indiv. Tng.	1958
710.10	Svc. Sch. Clerk	1954
711	Clerk Typist	1955
711.10	Clerk Typist	1954, 1960

MOS #	Job Title	Years
6.00	Personnel Specialist	1955, 1959
716.10	Company Clerk	1954
717	Admin. Specialist	1954
729	Pioneer Basic Engineer	1944
734	Half-track Driver	1943
736	Driver; Natl. Guard	1943, 1944
738	Intercept, High Speed	1944
740	Radio NCO	1947
745	Rifleman; Squad Ldr.	1941-46, 1952
746	Automatic Rifleman	1944
747	Airplane & Eng. Mechanic	1943-45
	Airplane Mech. Gunner	1946
750	Airplane Crew Chf; Airplane Flight Chief	1944-45
754	Radio Mechanic	1942-43, 1945
756	Radio Opr. Mech.	1943-44, 1948
757	Radio Opr. Mech.; ROM Gunner	1941, 1943-44, 1947
761	Scout; Liaison	1942-43
762	Airplane Engine Mech.	1943
762-6	Engine Mechanic	1943
766	Radio Opr., High Spd. Manual	1944
768.10	General Supply Spec.	1957
773.10	Ord. Parts Spec.	1957
776	Radio Opr.	1943-44
786	Toxic Gas Handler	1943
795	Messenger	1945

Army

7

MOS #	Job Title	Years
801	Cryptographic Machine Maint.	1948
803	Bugler	1939, 1943
805	Cryptographic Tech.	1944
807	Cryptographer	1943
809	Decontaminating Equip. Opr.	1944
810.00	Draftsman (Plans)	1955
811.10	Const. Draftsman (Plans)	1956
812	Heavy Weapons NCO	1943-44
813	Motor Transport NCO	1943
821	Supply NCO	1942, 1944-45 1951
835	Supply Clerk; Shipping Clerk	1943-46, 1949, 1951
844	Chief of Sec., Cannoneer; Gun Crewman, Lgt. Artillery	1945, 1948
848	Parts Clerk, Armament	1945
855	Dental Technician	1942
858	Medical Lab. Technician	1942
861	Surgical Tech.	1943-44, 1946
864	Gun Crewman, Med. Artillery	1945
903	Small Arms Weapons Mech.	1946
904	Machine Gun, Mech.	1943
911	Aircraft Armorer	1944, 1946
914	Artillery Mech. Hvy.	1944
931	Truck Driver Hvy.	1944-45
932	Special Vehicle Opr.	1945
937	Rifleman Instructor	1942
50.00	Security Guard; Interior Grd.	1955-56, 1961

MOS #	Job Title	Years
951.00	Basic Tng.; Military Police	1954
951.3	Pack Crewman Motorized	1944
965	Auto Mechanic	1944
979	Chemical Warfare Man General	1946
0006	Student Officer; Basic Tng.	1951, 1953, 1957, 1959
0007	Basic Soldier	1951
0521	Basic Tng.	1950
0629	Student	1951
0641	Lineman	1950
0835	Clerk Supply	1949
1014	Chief Wheel Vehicle Mech.	1948, 1953
1025	Student	1953
1172	NS	1942
1180	Platoon Leader	1960
1187	Repeaterman	1951, 1955
1290	Personnel Mgmt. Spec.	1954
1328	Platoon Commander; Adjutant	1940
1331	Platoon Engr.,Unit Commander	1944-45
1400	Machine Accounting Spec.	1953
1502	Administrative NCO (Clerk)	1954
1521	Basic Tng.	1950
1524-9	AT Platoon Ldr., Inf.	1943
1542	Infantry Officer; Inf. Unit Cmdr.	1942
1605	Heavy Weapons Crewman	1944
1607	Ammo Bearer; 81 Mortar	1946
1709	Radio Traffic Anal.	1952
1729	Comb. Construction Spec.	1953
1745	Basic Tng., Lgt. Wpns. Infman.	1952-53

Army

MOS #	Job Title	Years
1795	Tanker	1952, 1954
1814	Inf. Operations & Int. Spec.	1954
1824	Cook	1951-52
1844	Cannoneer (Converted)	1952
2162	Assists Regimental S-3 (Supervises Opn. of); Opns. & Tng. Staff Officer	1945
2187	Student	1951
2200	Personnel Officer - Military	1944
2260	Assistant S-3	1954
2320	Liaison Officer	1942
2356	Laborer	1950
2600	Admin. Asst.	1943
2601	Gun Crew Antiaircraft; Cannoneer Antiarcrft. Artillery	1943-44
2622	Unit Officer, Tng. Con. (Asst. S-3)	1951
2700	Student Officer; Student	1940, 1942, 1944, 1951
2736	Med. Tank Crewman	1945
2741	Orientation Spec.	1946
2750	Aerial Engineer	1944
3060	Cook	1949, 1952
3078	Electrician	1953
3164	Plumber	1951
3166	Student	1951
3290	Pers. Mgmt. Spec.	1951
3333	Dispensary Tech.	1950
3504	Clerk Ammo.	1950

Army

MOS #	Job Title	Years
3603	Antiaircraft Cannoneer	1952
3649	Student	1952
3729	Combat Const. Spec.	1952
3835	Supply Records Clerk	1951
3844	Cannoneer	1951
3912	Auto Fuel & Elec. Repmn.	1952
4000	Supply Ordnance, General	1944
4113	MTO Supply Officer; Mess Supply & Transp. Officer	1944-45
4121	General Utilities Rprmn.	1951
4345	Light Vehicle Driver	1952, 1954
4405	Clerk Typist	1951, 1953-54
4451	Center Commander	1945
4505	Ammo Supply Spec.	1951
4512	Ordnance Officer	1943
4514	Artillery Radar Opr.	1949
4532	Aviation Ordnance	1944
4641	Field Wireman	1950
4745	Basic Tng., Rifleman (Lgt. Wpns)	1951-52
4812	Hvy. Weapons, Infantry	1950
4844	Cannoneer	1950
4880	Executive Ofc., Finance Officer	(date not shown)
5356	Fireman, Furnace	1950
5832	Supply Handler	1951
6000	Basic Tng.	1952
7010	Asst. Div. Engineer	1944
7110	Construction Engr.	1945

Army

MOS #	Job Title	Years
7120	Company Officer; Utilities Ofcr.	1944, 1950
7130	Company Officer, Post Engr.	1942, 1945
7340	Anal. Chemical	1942
7360	Chemical Munitions Dev. Officer	1943
7610	Antitank Gun Crewman	1946
7745	Rifleman	1944
7835	Supply Clerk	1947
8103	Assistant Judge Advocate	1944
9301	S-2	1945
9312	Reconnaissance Officer	1944
9314	Cml., Int. Field	1945
None Given	Acting S-4	1944
" "	Adjutant	1944
" "	Aerial Gunnery	1943
" "	Asst. Division Engineer	None given
" "	Asst. S-3	1944
" "	Cannoneer	1943
" "	Engine Mechanic	1942
" "	Executive Officer	1944
" "	Flight Leader	1945
" "	MM 105 How. Crewman	1943
" "	Inspector Cml. Warfare (Officer)	1945
" "	Pilot	1945
" "	Platoon Commander	1942,43
" "	Platoon Officer	1944
" "	Stock Clk. (Arplne. & Auto Prts)	1943

AIR FORCE

MOS #	Job Title	Years
000.10	Basic Tng.	1955, 1957-58, 1961
059	Construction Tech.; Unit Foreman	1945
177	Radio Repairman	1942
275.6	Radio Opr. Mech.	1942
320.10	Student	1961
322.31 F	Student	1962
322.51 F	Weapons Cont. Sys. Mech.	1962
324.30	Precision Mea. Equipt. Spec.	1959
431.31 A	App. Aircraft Mechanic	1956
431.31 B	Aircraft Mechanic (Student)	1955
431.51	A/C Mechanic	Not given
431.51 B	A/C Mechanic (Over 2 Engs.)	1956
460.10	Student	1958
462.30 A	Student; Apr. Weapons Mech.	1958-59
462.50	Weapons Mechanic	1959
674	Messenger Center Chief	1942
682.3	Apr. Mach. Acc.	1955
705	Switchboard Operator	1942
760	Radio Operator	1945
771.30	Security Guard Helper	1958
771.50	Air Policeman	1954, 1961
791	Air Operations Specialist	1944
816	Asm. Technician	1947
826	AAF Supply Technician	1945-51
901	Munitons Handler	1944
902.32	Student (Crs. ABR 90232)	1962

Air Force

MOS #	Job Title	Years
902.52	Operating Room Spec.	Not given
953	Radar Repairman	1948
960	RCT Mechanic (Remote Con. Tur.)	1947
0001	Cas. Patient (no duty assgned)	1942, 1949, 1960
0003	Patient	1946
0141	Electronics Officer	1945
0200	Commanding Officer, Sq. Com. Off., Process/Lv./Tvl. C.O., Casual, Redeployment C.O.	1944-45
0205	Asst. Gp. Commun. Officer	1951
0251	Sr. Radar Mechanic	1950
0600	Basic Tng, Base Mtr. Officer	1943, 1950
1042	Personnel Equipt. Officer	1945
1051	Pilot	1942, 1945
1054	Pilot, Single Engine	1944
1055	Ftr. Pilot, Single Eng.	1943
2110	Gp. Adjutant (Hosp.)	1947
2120	Exec. Off. Airdrome Gp.	1947
2136	Co. Officer (Commander)	1941
2756	Radio Opr. Mech.	1944, 1946
3054	Asst. Gp. Commun. Officer	1952
4010	(S-4) Aircraft Maint.	1948
4805	Motor Maint. Officer	1941, 1944
4823	Aircraft Engineering Off.	1942
7536	Tech. Insp., Asst. Suprv. Acft.	1944-45
00010	Basic Airman	1955, 1957-58, 1961
27130	Airplane Air Opns. Spec.	1953
29230	Airplane Crypto Opr.	1953

Air Force

MOS #	Job Title	Years
29370	Radio Opr. Supv.	1951
30100	Asst. Gp. Commun. Officer	1951
32320	P/App. Tr. System Mech.	1946-58
42330	A/C Elec. Repairman	1955
60150	Sr. Air Tran. Spec.	1954
60330	App. Vehicle Opr.	1955
60350	Vehicle Opr.	1955
64010	Supply Helper	1957
64131	App. Org. Sup. Spec.	1957
90010	Student	1962
90232	Student (Crs. ABR 90232)	1962
90252	Oprtng. Rm. Spec. (Med. Wrd.), Corpsman (OB Wrd.), Opr. Rm.Spec.	1962, 1964
Not given	Radio Instructor	1943
Not given	Student	1941

Additional Lists

ARMY

MOS #	Job Title	Years
015.30	Electrical Engr. Asst.	1957
123	Nurse Male	1944
127	Battery Aid	1944
309.30	Electrical Engr. Asst.	1962
527	A A Fire Director Oper.	1943
528	Airplane Hydraulic Mech.	1944
555.70	Platoon Sgt.	1956
693	Instr. Oper.	1944
719	Oxygen Generation Plant Oper.	----
755	A A F Radio Oper. & Mech.	1944
768.70	Gen. Sup. Spec.	1952
0001	Casual	1954, 1958
0055	Clerk S4	1949
0745	S.D. Off. Club	1949
1359	Const. Mach. Supv.	1950
1441	Section Leader	1946
1495	Parachutist	1943
1641	Wire Trainee	1953
1740	Radio Trainee	1953
1821	Unit Supply Spec.	1951
2120	Admin. Asst.	1954
2745	Sq. Leader	1949
2756	A.H.F. Radio Mech.	1944
3174	Field Radio Mech.	1953
3311	Asphalt Mach. Oper	1951

ARMY (Continued)

MOS #	Job Title	Years
3648	Field Radio Repairman	1951
3885	Asst. Salvage NCO	1951
7539	Ord. Proff. Off. Fire Con Br	1954
7601	Elec. Eng. Engr. & Dex.Test. Sec. F.C. Br.	1954
11107	Rifleman	1964
55451	Sr. Const. Equip. Opr.	1951
-----	RAD Repairman	1943

AIR FORCE

MOS #	Job Title	Years
1092	Combat Crew Training	1943
2161	Sqdn Leader	1944
9260	Flying Safety Officer	1946

N A V Y

MOS #	Job Title	Years
642, 9-64	Aviation Machinist	1953
0011	Naval Reserve	1961
Not given	Aerographer's Mate Airman	1953
" "	Aerog. Mate 3rd class	1953
" "	Airman	1949, 1951-2, 1957
" "	Air Controlman Airman	1948
" "	Air Controlman 3rd Cl.	1949
" "	Airman Apprentice	1948, 1950-51, 1956
" "	Airman - Appr. Elec.	1952
" "	Aviation Boatswain's Mate	1946
" "	Aviation Boatswain's Mate (Arr. Gear & Bar.) 2nd Cl.	1946
" "	Aviation Boatswain's Mate 3/C (PH)	1945
" "	Aviation Cadet	1942
" "	Aviation Elec.'s Mate 2/C	1945 N.R.
" "	Aviation Elec.'s Mate 3/C	1944 N.R.
" "	Aviation Fire Controlman 2/C	1945
" "	Aviation Mach. Mate	1951
" "	Aviation Mach. Mate/Armn.	1951-2
" "	Aviation Mach. Mate/Airman Apprentice	1951-2
" "	Aviation Mach. Mate 2/C	1946
" "	Aviation Mach. Mate 3/C	1943, 1952
" "	Aviation Ordnance Man 3/C	1943
" "	Aviation Ordnance Man B2/C	1941, 1944
" "	Aviation Ordnance Man B3/C	1943

N A V Y (continued)

MOS #	Job Title	Years
Not given	Aviation Storekeeper 2/C (T)	1945
" "	Aviation Storekeeper 3/C	1944
" "	(Chief) Boatswain's Mate (AA) (T)	1945
" "	Boatswain's Mate 1/C	1944-5
" "	Boatswain's Mate 2/C	1943, 1945
" "	Boatswain's Mate 3/C	1950-1
" "	Cadet	1933
" "	Cargo Off. Ass't (additional duty)	1941
" "	Carpenter's Mate 3/C	1943, 1945
" "	Carpenter's Mate 2/C	1946
" "	Carpenter's Mate 3/C (T)(Builder)	1944
" "	Commissary 3/C	1948
" "	Communications Tech. 3/C	1953, 1960
" "	Communications Watch Officer (Duty)	1944-46
" "	Communications Technician Seaman	1952, 1957
" "	Constructionman	1957-63
" "	Coxswain	1942-3, 1945
" "	CTSN	1957
" "	CT 3	1960
" "	Deck Watch Officer (Duty)	1942, also not stated
" "	Deck Watch (Duty)	1940
" "	Disbursing Clerk	1949 N.R.
" "	E & O Clerk	1943
" "	Electrician/2	1955
" "	Electrician/3	1943, 1954
" "	Elec. Mate 2/C	1944, 1954
" "	Elec. Mate 3/C	1945, 1952

N A V Y (continued)

	MOS #		Job Title	Years
ng	"	"	Elec. Mate FA	1951
ng	"	"	Elec. Mate Pwr & Lght 3/C	1954
?	"	"	Electronics Tech. Apprentice	1951
?	"	"	Electronic Tech.'s Mate	1947
?	"	"	Electronics Tech.'s Mate 3/C	1945
?	"	"	Electronics Tech. Seaman	1952
?	"	"	Electronics Tech. Seaman Rcrt.	1951
?	"	"	Electronics Tech. 2/C	1954
?	"	"	Electronics Tech. 3/C	1950, 1953
ng	"	"	Engineer Officer	1945
ng	"	"	Engineer Officer (Ass't)	1940-44
?	"	"	Ensign	1940-41, 1943-44, 1951
?	"	"	ETSN	1951
ng	"	"	Examining Board	1945
high	"	"	Fire Controlman 1/C (T)	1942
high	"	"	Fire Controlman 2/C	1942, 1944
high	"	"	Fire Controlman 2/C (M)	1943
high	"	"	Fire Controlman 3/C	1941
ng	"	"	Fireman	1953
ng	"	"	Fireman 1/C	1943-6, 1944 N.R., 1953
ng	"	"	Fireman 2/C	1942-3, 1944 N.R., 1946
ng	"	"	Fireman 3/C	1943, 1943 N.R.
ng	"	"	Fireman Apprentice	1952
ng	"	"	Fireman 1/C Apprentice	1952
M	"	"	Fireman Specialist 1/C	1945
ng	"	"	Fueling Officer (Ass't) (Additional Duty)	1941
ng	"	"	Specialist (Fireman) 2/C	1944

N A V Y (continued)

MOS #	Job Title	Years
Not given	Spec. (Fireman) 3/C	1943
" "	Gunner's Mate G 3/C	1961, 62
" "	Gunner's Mate (Mount) 2/C	1946, 1950, 1952, 1962
" "	Gunner's Mate 3/C	1943, 1945, 1950, 1955
" "	" " 1/C	1942
" "	Hosp. Apprentice 1/C	1946
" "	Hosp. Apprentice 2/C	1945-6
" "	HSAA	1951
" "	HSAR	1951
" "	HSSR	1950
" "	Hull Board (add'l duty)	1945
" "	Interpreter - Lt. (jg.)	Not given
" "	Lieutenant	1943, 1948
" "	Lieutenant (AVN.)	1946
" "	Lt. Commander	1945
" "	Lt. (Exec. Officer)	1946
" "	Lt. (jg)	1942, 1944-6
" "	Lt. (jg) (Avn)	1944
" "	Lt. (jg) D-V (G)	1943
" "	Lt. (jg) I-V(S)	1942
" "	"M" Division Officer	1943
" "	Mach. Mate 1/C	1943 N.R.
" "	Mach. Mate 2/C	1942 N.R., 1946
" "	Mach. Mate 3/C	1944, 1946
" "	Mach. Mate (Gen. Mech.) Fireman Apprentice	1952
" "	Medical Officer - Jr.	1944, also not stated
" "	Medical Officer - Sr.	1944, also not stated

N A V Y (continued)

MOS #	Job Title	Years
Not given	Midshipman	1943-44, 1953
" "	Motor Mach. Mate 1/C	1945
" "	Motor Mach. Mate 2/C	1943, 1946
" "	Motor Mach. Mate 3/C	1944
" "	Musician 2/C	1945
" "	Musician 3/C	1944
" "	Personnel Man A (Records Clerk) 3/C (Reserve Duty)	1955
" "	Personnel Man A (Records Clerk) Seaman Non-rated	1954
" "	Personnel Man - Seaman non-rated	1952
" "	Pharmacist Mate 3/C	1946
" "	Port Deck Watch (add'l duty)	1941
" "	Quartermaster-Signalman 1/C	1948, 1950
" "	Radarman 3/C	1952
" "	Radarman Seaman Apprentice	1949
" "	Radarman Seaman non-rated	1950
" "	Radioman 1/C	1945
" "	Radioman 2/C	1944-5, 1962
" "	Radioman 3/C	1943-5, 1962
" "	Radioman Seaman Apprentice	1959
" "	Radioman Seaman non-rated	1960
" "	Radioman Seaman 2/C	1943
" "	Radio Tech. 3/C	1945
" "	Seaman	1952
" "	Seaman - Apprentice	1931, 1934-6, 1938, 1939, 1941-6, 1943 N.R., 1949-52, 1954, 1956, 1957, 1959

N A V Y (continued)

	MOS #	Job Title	Years
	Not given	Seaman - Apprentice - SV6	1944-6, 1952
?	" "	Seaman - Apprentice V12	1944-5
?	" "	Seaman 1/C	1936, 1939, 1941-7
?	" "	Seaman 1/C (EM)	1944
?	" "	Seaman 1/C (RT)	1944
?	" "	Seaman 1/C (Y)	1943, 1945
?	" "	Seaman 2/C	1931, 1935, 1937-8, 1941-7
ng	" "	Post Office Audit Board (add'l duty)	1944
?	" "	Seaman - non rated	1948, 1952-3, 1955-7, 1959
?	" "	Seaman Recruit (Same years Reserve)	1948-9, 1951-2, 1954-6
ng	" "	Ship Fitter 1/C	1945
ng	" "	Ship Fitter 2/C	1943
ng	" "	Ship Fitter 3/C	1941-2
ng	" "	Ship's Secretary	Not given
low	" "	Signalman 1/C	1941, 1944-5
low	" "	Signalman 2/C	1943-4, 1946
low	" "	Signalman 3/C	1941-2, 1945
ng	" "	Sonarman 3/C	1943
ng	" "	Sonarman (Harbor Def.) 3/C	1944
ng	" "	Soundman 2/C	1944
ng	" "	Soundman 3/C	1943
ng	" "	Specialist (Q) (IN) 1/C	1944
ng	" "	Specialist (I) 2/C (T)	
no	" "	Specialist (I) 3/C	1944
no	" "	Storekeeper 2/C	1943, 1945
no	" "	Storekeeper 3/C	1937, 1943-44
no	" "	Storekeeper - Disbursing 3/C	1945
no	" "	Storekeeper (Temp.) 3/C	1945

N A V Y (continued)

	MOS #	Job Title	Years
nf	" "	Storekeeper 3/C (T) (CB)	not stated
nf	" "	Storekeeper 3/C (SK 3/C)	1943-44
nf	" "	Torpedoman's Mate 3/C	1955
nf	" "	TMT 3/C	1955
nf	" "	Watch Officer	1940
nf	" "	Water Tender 3/C (T)	1944
nf	" "	Yeoman 2/C (T)	1943-4, 1946
nf	" "	Yeoman 3/C	1944
nf	" "	Yeoman 3/C (T)	1942, 1945

C O A S T G U A R D

	MOS #	Job Title	Years
	Not given	Cadet	1933
nf	" "	Radio Technician 1st Class	1944
nf	" "	Radio Technician 2nd Class	1943
nf	" "	Radioman 1st Class	1943
nf	" "	Radioman 2nd Class	1942, 1943
nf	" "	Radioman 3rd Class	1941, 43, 44
nf	" "	Seaman - Apprentice	1939, 42
nf	" "	Seaman 1st Class	1943
no	" "	Seaman 2nd Class	1939, 43

From Commander Tyler 2/7/72

MARINE CORPS

MOS #	Job Title	Years	
Not given	Controller	1944	none
Not given	Interceptor 2nd Cl.	1945	none
240	Tire Repairman (Prim)	1945	none
244	Tractor Driver	1944	none
528	Hydraulic Mechanic, Aircraft	1947	none
533	Demol SPL	1942	none
604	Light machine gunner	1944	none
606	Anti Aircraft Machine Gun	1945, 1944	none
639	Quartermaster Supply Chief	1946	none
747 A	Mechanic Aircraft	1947	none
759	VHF Radio Maint. & Repair	1944	maybe low
774	Airborne Radar Tech.	1945	moderate
0115	Radar Officer Ground Equipment	1944	high
0300	Ammo Carrier, M G Plt.	1953	none
0302	Infantry Officer	Not given	none
0331	Squad Ldr. MG Gunner	1954	none
1300	Basic Engr.	1950	none
1542	Infantry Officer	1943	none
2511	Oper. Communications Man	1961	none
30000 3000	Student Supply School	1953	none
3011	Unit Stockman	1955	none
3019	General Supply Chief	1949	none
3026	Engr. Stockman	1950	none
3029	Assistant Supply Chief	1950	none
3049	Clothing Supply Chief	1953	none
3500	Student	1950, 1953	none

MARINE CORPS - (continued)

MOS #	Job Title	Years	
3516	Auto Mechanic	1951, 1952	none
4011	E. A. M. Operator	1950	none
4100	PX Sales Clerk	1952	none
4131	Money Collector	1953	none
9900	Under Recruit Training	1950, 1953, ~~1952~~, 1951	none
	Basic Marine	1957, 1959, 1952	none

Supplemental List

MARINES

MOS #	Job Title	Year	
521	Basic	1944	none
522	Guard	1944	none
677	M.P.	1944	none
751	Engineering Chief Avn.	1946	none
775	Air Force Radio Oper.	1943	Low
776	Radio Oper.	1943	Low
843	Air Born Radar Oper.	1943	moderate
0311	"Duins"	1952	none
3513	Body & Fender Man	1953	none
3531	Truck Driver	1952	none
5811	Guard, NCO	1953	none
9900	Messman	1952	none

NATIONAL GUARD

MOS #	Job Title	Years
732	Driver, Tractor	1944
131.00	Armor Crewman	1962
940.00	Cook's Helper	1964
941.10	First Cook	1965

APPENDIX C-4

NAS SEARCH FORM FOR VALIDATION OF MILITARY SERVICE RECORD

APPENDIX C-4

NAS-NRC MILITARY ABSTRACT 1-1970

LEAVE THIS SPACE BLANK

Name

Last First Middle

Ser. No. Branch of Service

VA No.

Soc. Sec. No.

Education

Date of birth

mo. day year Race

Place of birth

State Country

MOS Code Title Date

LEAVE THIS SPACE BLANK

Organization Assignments Date

EAD date

Separation date

In Service Training Schools Date

Religion

Discharge rank

Service Outside Continental U.S.

Theater From To

APPENDIX D

APPENDIX D-1

MOTHER OF CHILD INTERVIEW

APPENDIX D-1

JOHNS HOPKINS UNIVERSITY
SCHOOL OF HYGIENE
ADULT & CHILD HEALTH SURVEY

Study No.________

FORM II - MOTHER OF CHILD

Mother's Name:____
Last First Maiden

Address:____
Street and No. City State County

Age:________ Date of Birth:__________ Place of Birth:____________________
mo. day year Hospital City State

Father's Name:____
Last First Middle

Address____
Street and No. City State County

Child's Name:____
Last First Middle

Address:____
Street and No. City State County

Sex of Child: ☐ Male Age of Child:________ Date of Birth:__________
mo. day year

☐ Female

Child's place of Birth:____________________________________
Hospital City State

Interviewer________________

Date of Interview________________

Study No.____________

FORM II - MOTHER OF CHILD

MARITAL HISTORY

I would like some information about your marriage (s).

How many times have you been married?__________ If never married, go to next page

Please start with FIRST marriage and then tell about later ones, if any, in chronological order

Name of Spouse Last First Middle	Year of Marriage	Outcome*	SPOUSE If living: Present Address	 If dead: Date City State	Blood Relation-ship +
1					No=1,Yes=2
2					No=1,Yes=2
3					No=1,Yes=2
4					No=1,Yes=2
5					No=1,Yes=2

* For Outcome Insert one of the following as applicable: Still married = 1, Divorced = 2, Separated = 3, Annulment = 4, Death = 5, Other (Specify)

\+ For Blood Relationship, ask: Were you and (your husband) related by blood, that is first cousins, second cousins? If no, circle(No=1)
If yes, circle (Yes=2) and write in "1st cousin", "2nd cousin", etc.

	"	"	Fireman Specialist 1/C	1945
	"	"	Fueling Officer (Ass't) (Additional Duty)	1941
	"	"	Specialist (Fireman) 2/C	1944

Study No._____,_____

REPRODUCTIVE HISTORY

I would like some information concerning your pregnancies and their outcome. How many times have you been

pregnant?__________ times.

Now, begin with your first pregnancy and continue in order. Tell me about All pregnancies regardless of outcome. (Interviewer: Star pregnancy involving index child.)

Pregnancy Order	Date Ended Mo/Da/Yr	Duration of Pregnancy*	Infant Born Alive Yes	No	Name of Child 1st, mid., last	Sex M or F	Place of Birth City	State	Hospital of Birth	Father Name	Address	Blood Rel. See Note
1.												
2.												
3.												
4.												
5.												
6.												
7.												
8.												

* Enter duration of pregnancy as number of weeks or number of months, specify which.

If Child is dead, record information immediately on following sheet.

If there are additional pregnancies, use extra sheet, change birth order numbers.

Note: Ask for each father - Were you and the father of this child related by blood? Insert Yes or No by father's name.

Study No._________

REPRODUCTIVE HISTORY (continued)

Current Status of Child

	IF LIVING:	IF DEAD:		
L or D	Address at present	Date of death	Place of death (Hospital, City, State)	Cause
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				

FORM II [illegible] OF CHILD — Study No. __

HEALTH OF CHILDREN

I would like to know if any of your children have ever had any of the following disorders.

(INSERT CHILDREN'S NAMES IN SAME ORDER AS GIVEN IN REPORDUCTIVE HISTORY - CHECK IF [illegible]

Child's Name	1	2	3	4	5	6	7	8	9	10	11
Heart Condition of any type											
Rheumatic Fever											
Thyroid Disease											
Leukemia											
Anemia											
Other Blood Diseases											
Birth Defects											
Gland Diseases											
Nervous Disorders											
Speech & Hearing Defects											
Eye Defects											
Epilepsy or Convulsions											
Mental Illness											
Mental Retardation											
Tumors											
Cancer											
Hospitalizations											

*For hospitalizations, specify name, place, date, and physician.

____

____

____

Study No. ________

HEALTH OF CHILDREN (Continued)

For each child where any of the illness mentioned on previous page is **yes**, ask the following:

Birth Order	Name of Child	Disorder	Age of Onset	Year of Onset	Hospital, if any, &/or Physician and Treatment

Study No. ______________

FORM II - MOTHER OF CHILD

RADIATION EXPOSURE 1.

I would like to ask you some questions about yourself. Firstly, exposure to X-Rays or other types of radiation.

A. Do you ever recall having X-Rays for any of the following?

Part of Body X-Rayed	Yes	No	IF YES: Name of Hos. or Doctor (Street, City, State)	What Year
1. Chest, except mobile unit				
2. Stomach and intestines - including barium i.e. GI series				
3. Kidneys including I.V.P.				
4. Gall Bladder				
5. Arms and legs, incl. fractures				
6. Spinal Column				
7. Head				
8. Bladder				
9. Uterus				
10. Pelvis				
11. Other organs				
12. (Specify)				

Study No. ___________

FORM II - MOTHER OF CHILD

RADIATION EXPOSURE 2.

B. Do you recall having had X-Rays or radiation treatment for any of the following?

	Yes	No	IF YES: Name of Hospital or Doctor (St., City, State)	What Year
1. Skin trouble				
2. Warts or birth marks				
3. Excess menstrual bleeding or other female disorders				
4. Thyroid				
5. Thymus				
6. Adrenals				
7. Too much Blood (Polycythemia)				
8. Tumors				
9. Sinus Trouble				
10. Rheumatism or Arthritis				
11. Bursitis				
12. Jaw or mouth				
13. Other (specify) ___________				

FORM II - MOTHER OF CHILD

Study No. __________

RADIATION 3.

C. Did a doctor ever use a flouroscope machine to examine you (i.e. looking at your heart or lungs or intestines through a screen in a dark room.) /_/ Yes /_/ No /_/ Don't know

IF YES:

What part of Body	For what illness, injury, or symptoms	Year	Where: City, State, Hospital	Doctor's Name

D. Have you ever had a job where you worked with or near radiation, either X-Rays or other forms? /_/ Yes /_/ No /_/ Don't know

IF YES: Beginning with the first job you recall and proceeding to the most recent: (IN CHRONOLOGICAL ORDER)

Year	Place	Type of Employment Company's Name	Describe Duties	Duration of Duties	
				From	To

E. Have you ever worked with radar? or microwave? /_/ Yes /_/ No Near a radar installation? /_/ Yes /_/ No

IF YES: Beginning with the first job you recall and proceeding to the most recent: (IN CHRONOLOGICAL ORDER)

Year	Place	Type of Employment Company's Name	Describe Duties	Duration of Duties	
				From	To

FORM II - MOTHER OF CHILD

Study No. ________

RADIATION 4.

E. Have you ever had radioactive materials injected into your veins or abdomen for diagnosis or treatment of any condition?

/_7 Yes /_7 No /_7 Don't know

F. Have you ever drunk radioactive materials so that the doctor could see if your thyroid or some other organ was all right? (also called atomic cocktail, trace-studies, labeled matabolic studies).

/_7 Yes /_7 No /_7 Don't know

IF YES: To either of both question (E.) or (F.), answer question (G.).

G. I would like to obtain some details about these procedures. Now in order, starting with the EARLIEST FIRST:

Year	Material used*	How Administered: (drug, pill, injection under skin, from machine)	What part of body was treated or exposed to radiation	For what illness or symptoms was this given	How many times was this given	Doctor's name - address (city, state, hospital)

*Any of the following: I-131 Co 60 Gold Cobalt Thorotrast Other (specify, if known)
P 32 Radium Iron Carbon - 14 Chromium - 59

Study No. ___________

FORM II - MOTHER OF CHILD

HOSPITALIZATION

I would like to find out about any hospitalization you have had in your life whether it was for diagnosis, medical treatment, or surgery.

(Please exclude hospitalization directly connected with the birth of a child or a miscarriage.) These have been reported already on the previous pages.

Now, starting with the FIRST:

Year	Name of Hospital (City and State)	Reason for Admission	If surgery or operation performed, name or describe	Name and Address of Doctor
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				
11.				
12.				
13.				
14.				

Study No. ________

FORM II - MOTHER OF CHILD

ILLNESS (personal):

I would like some information about illnesses you may have experienced during your lifetime.

A. Do you have any birth defects or malformations that have been present since birth?

Don't know /__/ No /__/ Yes /__/ IF YES: Specify ____________________

B. Have you ever had any of the following disorders:

	Yes	No	Don't Know	IF YES: What year was it diagnosed	Did you receive medical treatment	IF YES: Please give doctor's name and address	
						Doctor's Name	Address: St., City, State
Thyroid disease							
Diabetes							
Adrenal disease							
Liver disease* ____________							
Nephritis or other Kidney diseases							
Tuberculosis							
Disease of ovaries, uterus, or female organs							
Rheumatic Heart Disease							
Cancer (specify site or organ)____________							

*Specify type, if possible.

Study No. _______

FORM II - MOTHER OF CHILD

ILLNESS (personal): continued

	Yes	No	Don't know	IF YES: What year was it diagnosed	Did you receive medical treatment	IF YES: Give doctor's name and address	
						Doctor's Name	Address-St., City, State
Tumor (non malignant)* ____________							
Chicken Pox							
German measles							
Mumps							
Poliomyelitis							
Blood Diseases, any kind							
Hypertension							
Convulsions or Epilepsy							
Visual or Hearing Defects							
Leukemia							
Anemia							

*Specify site.

FORM II - MOTHER OF CHILD

Study No. ______

MENSTRUAL HISTORY

A. At what age did you have your first period? ______yrs.

B. What is (was) the usual 'uration in days? ______days

C. How many days from the first day of one period to the first of the next? ______days.

D. Have you ever had difficulties with your period that cuased you to be concerned and seek medical advice?

/_/ Yes /_/ No

IF YES:

Year	Age	Symptom	Physician's Name	Physician's Address

E. Are you still having your periods? /_/ Yes /_/ No

IF NO:

1. How old were you when they stopped? ______yrs.
2. Did they stop naturally of their accord? /_/ Yes /_/ No

IF YES: How long a time passed from the first change until there was no more bleeding? ___mos. ___yrs

IF NO: (a) What caused them to stop? /_/ operation /_/ X-Ray or radium /_/ hormone pills /_/ other

(b) Name of doctor who treated you: ______________________

Address: ______________________

Hospital: ______________City______State______

FORM II - MOTHER OF CHILD

Study No. ____________

MEDICATIONS

Have you ever used or taken any of the following medications?

	Yes	No	DK	IF YES: What Year	How Long	Reaction*	Doctor or Hos. Where Medication Prescribed: Name	Address
Hormones: Cortisone, ACTH, progesterone, stilbesterol, estrogens, testosterone, Metandren, premarin, prolutin, valestril, pranone, etc.								
Thyroid								
Tranquilizers								
Barbiturates (phenobarbitol, luminol, **seconal, nembutol, donnital)**								
Pep pills or dexedrine								
Pills or shots for pain (specify kind)								
Other Medicines								
Oral Contraceptives ~~birth control pill~~ (enovid, orthonovum, norlestrin, nornyl) "the pill"								

How often do you take aspirin? ____________________

*Reaction - write: None, Rash, Swelling Nausea, Vomiting, Diarrhea, Other

FORM II - MOTHER OF CHILD

Study No _______

OCCUPATION

A. What do you usually do during the working hours? (check one or more)

Work full time /__/ Keep house /__/ Retired /__/ Other /__/ (If other, specify) ________

Work part time /__/ Go to school /__/ Disabled /__/

B. If not working now, have you ever worked for pay? /__/ Yes /__/ No

C. IF YOU HAVE WORKED: I would like to know what kind of jobs you have had including part time, Armed Service jobs, starting with your present (OR LAST) job FIRST.

Name of Company	What does Company do	What did you do	What was job title	Time at That job: from	to	If health was one of your reasons for leaving please Explain:
1.						
2.						
3.						
4.						
5.						
6.						
7.						
8.						
9.						

FORM II - MOTHER OF CHILD

Study No.___________

EDUCATIONAL HISTORY

A. What was the highest year of school you completed? (Circle one)

0 1 2 3 4 5 6 7 8 9 10 11 12 or more

B. If 12 or more, describe type of school below. (START WITH THE SCHOOL AFTER HIGH SCHOOL)

Type of School	Name of School	Address	Degree	Year
1.				
2.				
3.				
4.				

RELIGION

A. What is your religious preference?

Roman Catholic /__/ Jewish /__/ Greek Orthodox /__/

Protestant /__/ Specify denomination: ______________________________

B. Do you belong to a church or synagogue? Yes /__/ No /__/

C. Do you attend: /__/ Regularly (2-3 times a month or more).

/__/ Occasionally or rarely.

/__/ Never (less than once per year).

FORM II - MOTHER OF CHILD

Study No. ____________

RESIDENCE HISTORY

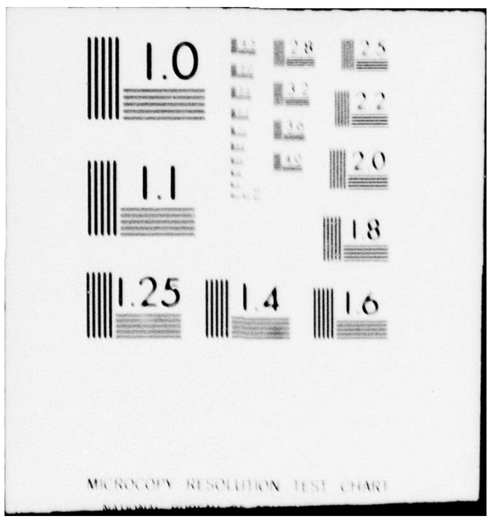
Name of City or Town	State or Foreign Country	Address (if remembered)	During which years did you live there?	
			From	To

AD-A061 593   JOHNS HOPKINS UNIV BALTIMORE MD SCHOOL OF HYGIENE A--ETC F/G 6/18
PARENTAL RADIATION AND DOWN'S SYNDROME, WITH PARTICULAR ATTENTI--ETC(U)
JUN 76 B H COHEN   DADA17-69-C-0154

UNCLASSIFIED   NL

5 OF 5
AD
A061 593

END
DATE
FILMED
2-79
DDC


1.0
2.8
2.5
3.2
2.2
3.6
4.0
2.0
1.1
1.8
1.25
1.4
1.6
MICROCOPY RESOLUTION TEST CHART

FORM II - MOTHER OF CHILD

Study No. ________

FAMILY HISTORY:

A. I would like to know some things about your family.

Now beginning with your father:

Relation to Mother of Case	Name: Last	First	Middle	Place of Birth	Date of Birth	Occupation	IF LIVING: Age	Address	IF DEAD: Age	Year	Place-City State, County	Cemetary
Father												
Mother												
Brothers & Sisters* 1.												
2.												
3.												
4.												
5.												
6.												
7.												
8.												
9.												
10.												
11.												
12.												

* If not related by blood indicate relationship e.g. step sister, half sister, half brother, step brother.

B. Were your father and mother related by blood? /__/ Yes /__/ No

IF YES: What degree of relation were they? ________________________

Study No. ____________

FORM II - MOTHER OF CHILD

THESE ARE ALL THE QUESTIONS THAT I HAVE.

DO YOU HAVE ANY QUESTIONS?

Thank you very much. You have been very helpful.

If you think of anything further that you forgot to tell me or would like to know, would you please give my supervisor a call at 732-2010, or 732-7374.

Interviewer's comments: ____

____

____

APPENDIX D-2

FATHER OF CHILD INTERVIEW

1

<u>FORM III - FATHER OF CHILD</u>

JOHNS HOPKINS UNIVERSITY
SCHOOL OF HYGIENE
ADULT & CHILD HEALTH SURVEY

Study No._____

Father's Name: ____
Last First Middle

Address: ____
Street and No. City State County

Age: ________ Date of Birth: __________ Place of Birth: ____________________
mo. day year Hospital City State

Mother's Name: ____
Last First Maiden

Address: ____
Street and No. City State County

Child's Name: ____
Last First Middle

Address: ____
Street and No. City State County

Sex of Child: ☐ Male Age of Child: ________ Date of Birth: ________
mo. day yr.

☐ Female

Child's place of Birth: ________________________________
Hospital City State

Interviewer ____________________

Date of Interview ____________________

FORM II.

STUDY NO. ________

MILITARY HISTORY

Have you ever served in the military or armed forces? _____ Yes _____ No _____ Don't know

IF YES

Rank

Which branch of the service? _____ Army _____ Navy _____ Marine Corps _____ Air Corps _____ Coast Guard

What was your military service number? ____________________

Date of Entry
Date of Discharge

	Yes	No	DK	IF YES, Duties
Were you ever stationed at an air field?				
Were you ever stationed at a radar park?				
Were you ever stationed at a missile site?				
Did you ever repair, maintain, operate, or test radar?				
Did you ever repair, maintain, operate or test microwave				
Did you ever repair, maintain, operate or test electronic products?				
Did you ever repair, maintain, operate or test radio communications gear?				
Did you ever serve on shipboard?				
IF YES: Was most of your duty above deck?				
Was most of your duty below deck?				
Did any of your military units use mobile radars?				

What were the names and numbers of the units to which you were attached?

Name and Number	Where	From	To	Duties

Study No. _____

FORM III - FATHER OF CHILD

RADIATION EXPOSURE 1.

I would like to ask you some questions concerning exposure to X-Rays or other types of radiation.

A. Do you ever recall having X-Rays for any of the following?

Part of Body X-Rayed	Yes	No	IF YES: Name of Hospital or Doctor (St. City, State)	Year
1. Chest, except mobile unit				
2. Stomach and intestines - including barium i.e. GI series				
3. Kidneys including I.V.P.				
4. Gall Bladder				
5. Arm and legs, incl. fractures				
6. Spinal Column				
7. Head				
8. Bladder				
9. Abdomen				
10. Pelvis				
11. Other Internal Organs				
12. (Specify)				

Study No. ______

FORM III - FATHER OF CHILD

RADIATION EXPOSURE 2.

B. Do you recall having had X-Rays or radiation treatment for any of the following

	Yes	No	IF YES: Name of Hospital or Doctor (St., City, State)	Year
1. Skin trouble				
2. Warts or birth marks				
3. Thyroid				
4. Thymus				
5. Adrenals				
6. Too much blood (Polycythemia)				
7. Tumors				
8. Sinus Trouble				
9. Rheumatism or Arthritis				
10. Bursitis				
11. Jaw or mouth				
12. Other (specify)				

Study No. ________

FORM III - FATHER OF CHILD

RADIATION 3.

C. Did a doctor ever use a flouroscope machine to examine you (i. e. looking at your heart or lungs or intestine through a screen in a dark room.) /__/ Yes /__/ No /__/ Don't know

IF YES:

What part of Body	For what illness, injury, or symptoms	Year	Where: City, State, Hospital	Doctor's Name

D. Have you ever had a job where you worked with or near radiation, either X-Rays or other forms?
/__/ Yes /__/ No /__/ Don't know

IF YES: Beginning with the first job you recall and proceeding to the most recent (IN CHRONOLOGICAL ORDER).

Year	Place	Type of Employment Company's Name	Describe duties	Duration of Duties	
				from	to

E. Have you ever worked with radar, or microwave? /__/ Yes /__/ No Near a radar installation? /__/ Yes /__/ No

IF YES: Beginning with the first job you recall and proceeding to the most recent: (IN CHRONOLOGICAL ORDER).

Year	Place	Type of Employment Company Name	Describe duties	Duration of Duties	
				from	to

Study No. _____

FORM III - FATHER OF CHILD

RADIATION 4.

E. Have you ever had radioactive materials injected into your veins or abdomen for diagosis or treatment of any condition?

Yes ☐ No ☐ Don't know ☐

F. Have you ever drunk radioactive materials so that the doctor could see if your thyroid or some other organ was all right? (also called atomic coctail, trace-studies, labeled matabolic studies).

Yes ☐ No ☐ Don't know ☐

IF YES: To either of both question (E.) or (F.), answer question (G.).

G. I would like to obtain some details about these procedures. Now in order, starting with the EARLIEST FIRST:

Year	Material used*	How Administered: (drug, pill, injection under skin, from machine)	What part of body was treated or exposed to radiation	For what illness or symptoms was this given	How many times was this done	Doctor's name-address (city, state, hos.)
	.					

*Any of the following: I-131 Co 60 Gold Cobalt Thorotrast Other (specify, if known)
P 32 Radium Iron Carbon - 14 Chromium - 59

Study No. ______

FORM III - FATHER OF CHILD

HOSPITALIZATION

I would like to find out about any hospitalization you have had in your life whether it was for diagnosis, medical treatment, or surgery.

Now, starting with the FIRST:

Year	Name of Hospital (City and State)	Reason for Admission	If surgery or operation performed, name or describe	Name and Address of Doctor
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				
11.				
12.				
13				
14.				

Study No. ______

FORM III - FATHER OF CHILD

ILLNESS (personal):

I would like some information about illnesses you may have experienced during your lifetime.

A. Do you have any birth defects or malformations that have been present since birth?

Don't know /__/ No /__/ Yes /__/ IF YES: Specify ________________

B. Have you ever had any of the following disorders:

	Yes	No	Don't know	If YES: What year was it diagnosed	Did you receive medical treatment	IF YES: Please give doctor's name and address: Doctor's Name	Address: street, city, state
Thyroid disease							
Diabetes							
Adrenal disease							
Liver disease*							
Nephritis or other Kidney disease							
Tuberculosis							
Disease of prostrate or male organs							
Rheumatic Heart Disease							
Cancer (specify site of organ)							
Tumor (non malignant)*							
Chicken pox							
German measles							

*Specify type, if possible

*Specify site

Study No. ________

FORM III - FATHER OF CHILD

ILLNESS (personal): continued

	Yes	No	Don't know	IF YES: What year was it diagnosed	Did you receive medical treatment	IF YES: Please give doctor's name and address	
						Doctor's Name	Address: street, city, state
Mumps							
Poliomyelitis							
Blood Disease							
Hypertension							
Convulsions or Epilepsy							
Visual or Hearing Defects							
Leukemia							
Anemia							

Study No. _______

FORM III - FATHER OF CHILD

MEDICATIONS

A. Have you ever used or taken any of the following medications?

	Yes	No	D. K.	What Year	How Long	Reactions*	IF YES: Doctor or Hospital where Medication Prescribed: Name	Address
1. Thyroid, iodine								
2. Other Hormones**								
3. Tranquilizers								
4. Pep pills or Dexedrine								
5. Pills or shots for pain (specify)								
6. Barbiturates (phenobarbitol, luminol, seconal, nembutal, donnital)								
7. Other Medicines (Specify)								

*Reaction - write: Rash, Swelling, Nausea, Vomiting, Diarhea, Other

**Cortisone or ACTH, Testosterone (Metandren), Stilbesterol, Progesterone, Premarin, Prolutin, Valestril, Pranone, etc.

Study No. ____

FORM III - FATHER OF CHILD

EDUCATIONAL HISTORY

A. What was the highest **year** of school you completed? (Circle one)

0 1 2 3 4 5 6 7 8 9 10 11 12 or more

B. If (12 or more), describe type of school below. (START WITH THE SCHOOL AFTER HIGH SCHOOL)

Type of School	Name of School	Address	Degree	Year
1.				
2.				
3.				
4.				

RELIGION

A. What is your religious preference?

Roman Catholic ☐ Jewish ☐ Greek Orthodox ☐

Protestant ☐ Specify denomination: ____________________

B. Do you belong to a church or synagogue? Yes ☐ No ☐

C. Do you attend; ☐ Regularly (2-3 times a month or more).

☐ Occasionally or rarely.

☐ Never (less than once per year).

Study No. ______

FORM III - FATHER OF CHILD

OCCUPATION

A. What do you usually do during the working hours? Check one or more.

Work full time ☐ Keep house ☐ Retired ☐ Other ☐

Work part time ☐ Go to school ☐ Disabled ☐ (If other, specify) ______

B. If not working now, have you ever worked for pay? ☐ Yes ☐ No

C. IF YOU HAVE EVER WORKED, I would like to know what kind of jobs you have had including part time, Army jobs, starting with your present (OR LAST) job FIRST.

Name of Company	What does Company do	What did you do	What was job title	Time at That job: From	To	If health was one of your reasons for leaving - EXPLAIN:
1.						
2.						
3.						
4.						
5.						
6.						
7.						
8.						

13 ~~#~~ ~~13~~

Study No. ________

FORM III - FATHER OF CHILD

RESIDENCE HISTORY

Name of City or Town	State or Foreign Country	Address (if remembered)	During which years did you live there	
			from	to

Study No. _____

FORM III - FATHER OF CHILD

MARITAL HISTORY:

I would like some information about your marriage(s).

A. How many times have you been married? _______ (If answer is NEVER, OR ZERO, SKIP PAGE 15a.)

B. Please START with the FIRST marriage and then tell about later ones, if any, IN CHRONOLOGICAL ORDER.

Name of Spouse			Year of Marriage	Outcome* (see below)	IF death of spouse is outcome, give:			If living either apart or together	Other perti-nent infor.
Last	First	Middle			Date	Cause	Place of death: City, State, Hos.	Present whereabouts City, State, St.	
1.									
2.									
3.									
4.									
5.									
6.									

*For OUTCOME Insert one of the following as applicable: still married, death of spouse, divorce, separation, annulment, other (specify)

FORM III - FATHER OF CHILD

Study No. ______

To Interviewer: Father interviewed alone ☐ Yes ☐ No Wife Present ☐ Others ☐

REPRODUCTIVE HISTORY

I would like some information about your children.

A. Tell me about all your children, living or dead.

No. of Child	Year of Birth	Infant alive at birth		Sex	Name of Child	Place of Birth	
		Yes	No			City and State	Hospital

B. Were you and mothers of any of these children related by blood? ☐ Yes ☐ No

IF YES:

Which of these mothers? ______

What is the relationship? ______

(i.e. first cousin, second cousin)

15D-T1

FORM III - FATHER OF CHILD

Study No. ______

REPRODUCTIVE HISTORY (cont.)

B. Continuing in the same order with the oldest child first, tell me about all of your children.

No. of Child	Mother's Name	Mother's Address	Any abnormalities of child at birth. IF YES: Describe	Child still living now:		IF NO: Give date, place and cause of death		
				Yes		Date	City and State	Cause

Study No. ____

FORM III - FATHER OF CHILD

FAMILY HISTORY:

A. I would like to know some things about your family.

Now beginning with your father:

Relation to Father of Index	Name: Last	First	Middle	Place of Birth	Date of Birth	Occupation	IF LIVING Age	Address	IF DEAD Age	Year	Place-City State Country	Cemetary
Father												
Mother												
Brothers and sisters (listed by birth order).*												
1.												
2.												
3.												
4.												
5.												
6.												
7.												
8.												
9.												
10.												
11.												
12.												

*If not related by blood indicate relationship e.g. step sister, half sister, half brother, step brother.

B. Were your father and mother related by blood? ☐ Yes ☐ No

IF YES: What degree of relation were they? ____

Study No. ______________

FORM III - FATHER OF CHILD

THESE ARE ALL THE QUESTIONS THAT I HAVE.

DO YOU HAVE ANY QUESTIONS?

Thank you very much. You have been very helpful.

If you think of anything further that you forgot to tell me or would like to know, would you please give my supervisor a call at 732-2010. or 732-7374.

Interviewer's comments: ____

____

____

APPENDIX D-3

FOLLOW UP INTERVIEW ON RADAR-MICROWAVE EXPOSURE FOR ORIGINAL SERIES (INCORPORATED IN CURRENT SERIES INTERVIEW)

1.

FORM IV - HISTORY

JOHNS HOPKINS UNIVERSITY
SCHOOL OF HYGIENE
ADULT & CHILD HEALTH SURVEY

Name: ____
Last First Middle

Address: ____
Street and No. City State County

Age: ________ Date of Birth: ______________ Place of Birth ______________________________
Mo. Day Year Hospital City State

Interviewer __________________

Date of Interview __________________

STUDY NO. ______________

MILITARY HISTORY

Have you ever served in the military or armed forces? _____ Yes _____ No _____ Don't know

IF YES

Which branch of the service? _____ Army _____ Navy _____ Marine Corps _____ Air Corps _____ Coast Guard

What was your military service number? ____________________

Date of entry:
Date of discharge:
Rank:

	Yes	No	DK	IF YES, Duties
Were you ever stationed at an air field?				
Were you ever stationed at a radar park?				
Were you ever stationed at a missile site?				
Did you ever repair, maintain, operate, or test radar?				
Did you ever repair, maintain, operate or test microwave?				
Did you ever repair, maintain, operate or test electronic products?				
Did you ever repair, maintain, operate or test radio communications gear?				
Did you ever serve on shipboard?				
IF YES: Was most of your duty above deck?				
Was most of your duty below deck?				
Did any of your military units use mobile radars?				

What were the names and numbers of the units to which you were attached?

Name and Number	Where	From	To	Duties

NON-MILITARY EXPOSURE

In your work outside military service, have you ever worked with radar, microwave, or electronic products? Circle One: Yes No DK

IF YES:

Name of company	Where	From	To	Duties

DISTRIBUTION LIST

4 copies	HQDA (SGRD-RP) WASH, DC 20314
12 copies	Defense Documentation Center (DDC) ATTN: DDC-TCA Cameron Station Alexandria, Virginia 22314
1 copy	Superintendent Academy of Health Sciences, US Army ATTN: AHS-COM Fort Sam Houston, Texas 78234
1 copy	Dean School of Medicine Uniformed Services University of the Health Sciences Office of the Secretary of Defense 6917 Arlington Road Bethesda, Md. 20014